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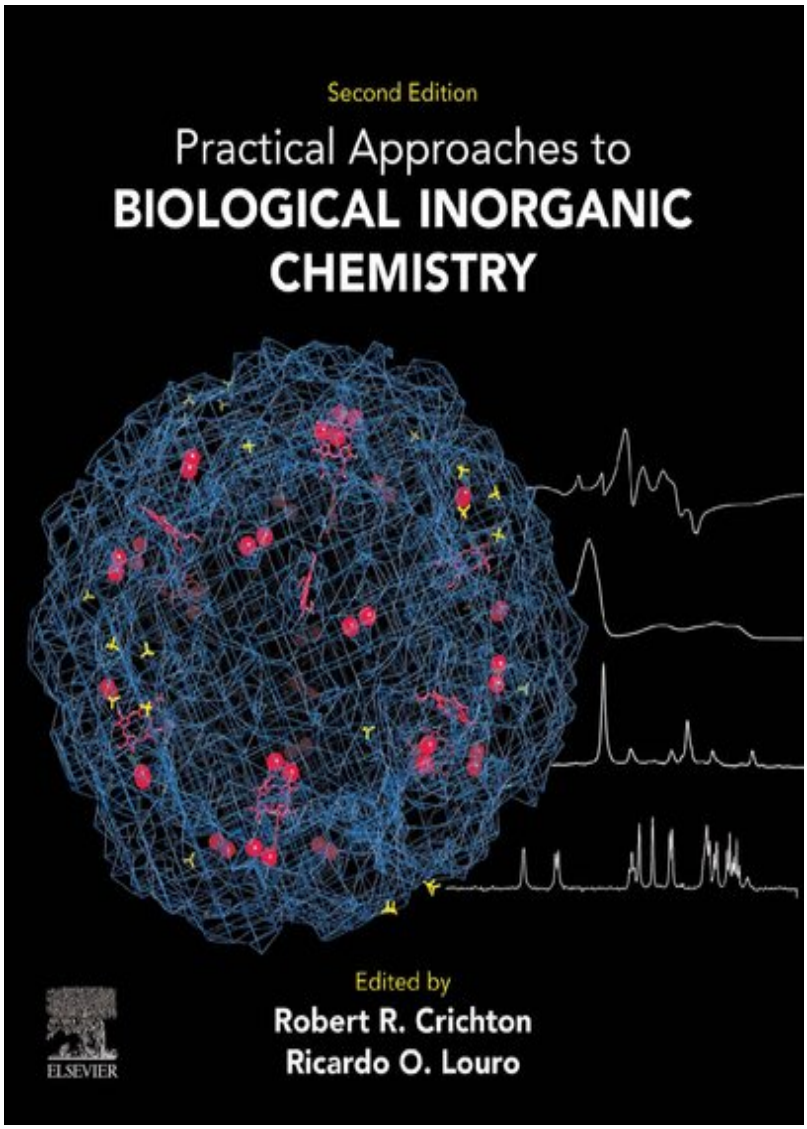

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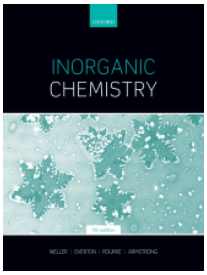

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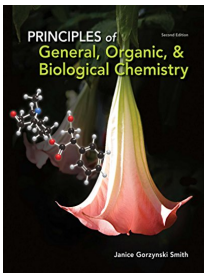

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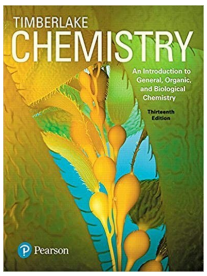

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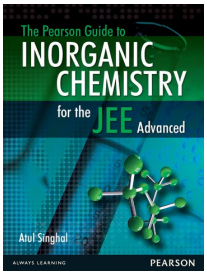

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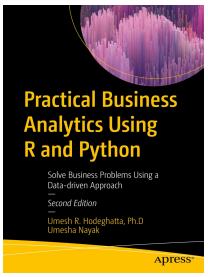

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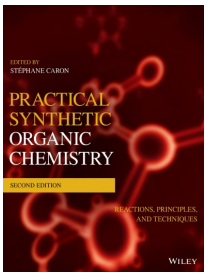

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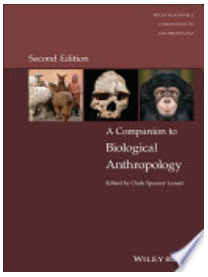

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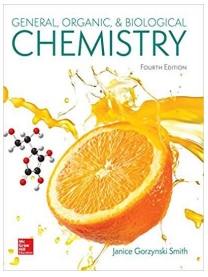

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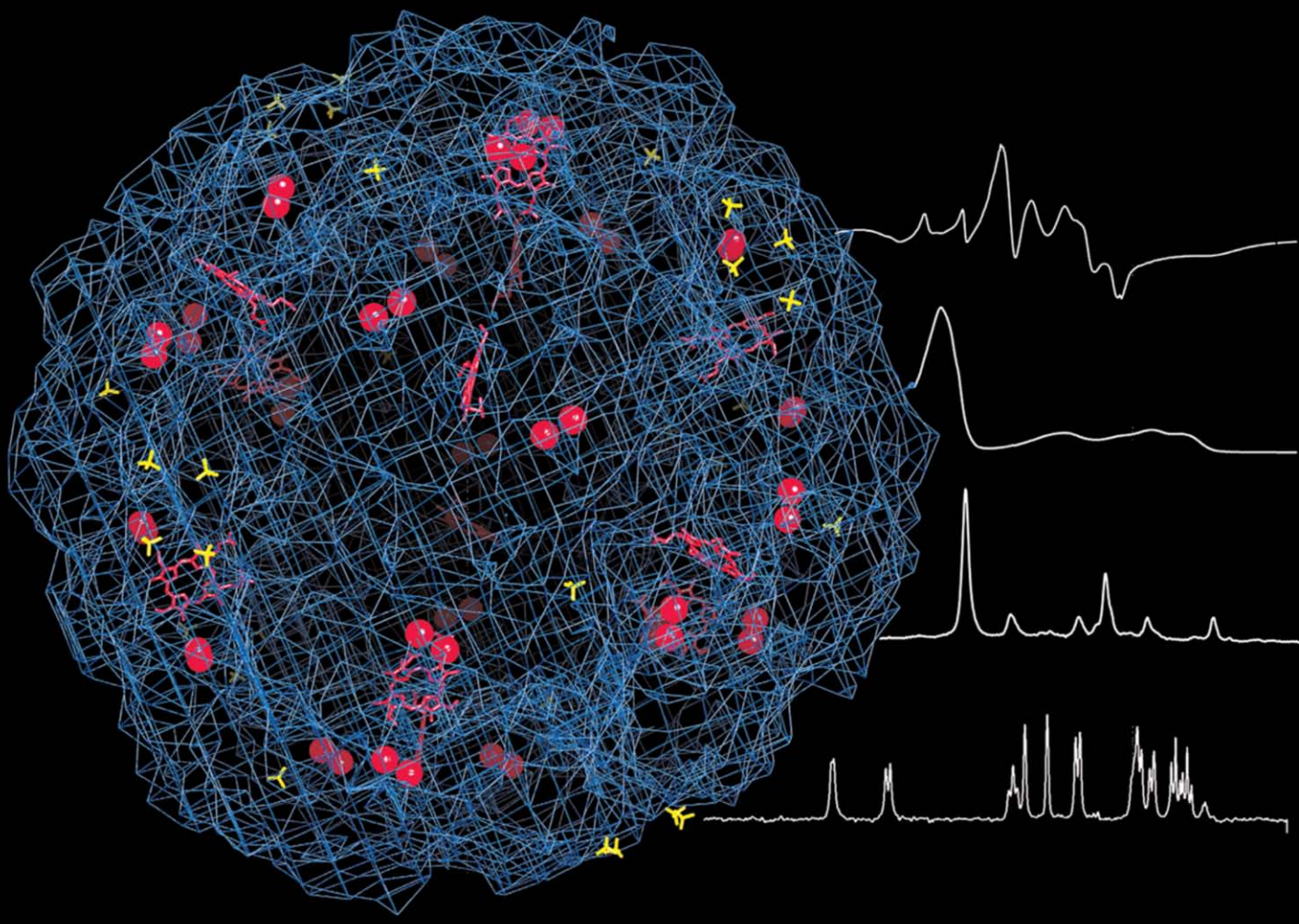

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PRACTICAL APPROACHES TO BIOLOGICAL INORGANIC CHEMISTRY

SECOND EDITION

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CHAPTER

1

An overview of the role of metals in biology

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OUTLINE

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Introduction

Metals play many different roles in the biological world, whether by their participation in essential biological processes, as toxic constituents of our environment, or as indispensable diagnostic and therapeutic agents in human medicine. Only a limited number of metal ions are essential for most living organisms (Fig. 1.1), and this short introduction begins by illustrating the biological importance of metals, not only in vital processes such as intermediary metabolism, electron transfer, respiration, and photosynthesis, but also in neurotransmission, cell signaling, apoptosis, and fertilization.

While many essential metals can be toxic, particularly when they are in excess, in our modern environment there are a number of nonessential metals, such as cadmium, lead, mercury, and aluminum, which are themselves highly toxic.

Finally, metals have assumed an extraordinary number of roles in medicine, not only therapeutically as drugs, but also as noninvasive contrast agents and radiopharmaceuticals.

More detailed accounts of these aspects of metal ions are presented in the companion volume to this second edition (Crichton, 2018).

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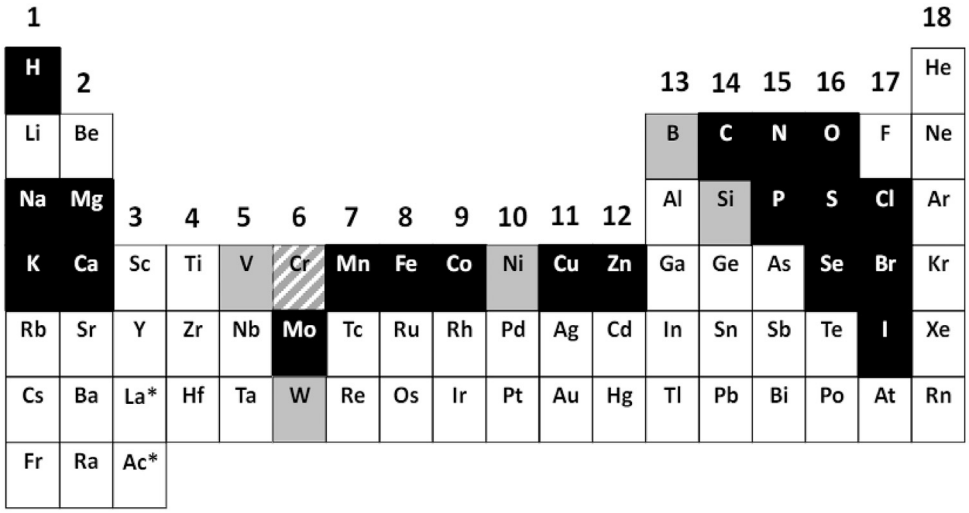

FIGURE 1.1 A biological periodic table of the elements indicating the essential elements. The essential elements for most forms of life are shown in black with the exception of chromium (Cr), which is shown with an upward diagonal pattern, and essential elements that are more restricted for some forms of life shown in gray. *Source: Reproduced from Maret, W., 2016. The metals in the biological periodic system of the elements: concepts and conjectures. Int. J. Mol. Sci. 17, pii:E66. doi:10.3390/ijms17010066. This is an open access article distributed under the Creative Commons Attribution License (CC BY) which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

Essential metal ions and their functions

Most living organisms require some 25 elements (Maret, 2016; Chellan and Sadler, 2015) including between 10 and 14 metal ions (Fig. 1.1). In the case of *Homo sapiens*, there are 10 essential metal ions (sodium, potassium, calcium, magnesium, manganese, iron, cobalt, copper, zinc, and molybdenum). Of these, the first four are considered as "bulk elements" (Na^+, K^+, Ca^{2+}, and Mg^{2+}), representing 112 g, 160 g, 1.1 kg, and 25 g, respectively, in an "average" person of body weight 80 kg (The data on the abundance of elements in the 80 kg human body are those given in WebElements: http://www.webelements.com/.). Together, they constitute some 99% of the metal ion content of the human body. The others, manganese, iron, cobalt, copper, zinc, and molybdenum, designated "trace elements," are present in much lower amounts than the bulk elements (respectively, 16 mg, 4.8 g, 1.6 mg, 80 mg, 2.6 g, and 8 mg in an 80-kg person).

The essential alkali metal ions Na^+ and K^+ only weakly bind organic ligands, rendering them extremely mobile, as with H^+ and Cl^-. This enables them to generate ionic gradients across biological membranes. The distribution of Na^+ and K^+ in mammals is quite different; Na^+, together with Cl^-, is the major electrolyte in the extracellular fluid, whereas K^+ is retained within the cells. The concentration of Na^+ in the plasma is maintained within narrow limits at about 145 mmol/L, and its intracellular concentration is only about 12 mmol/L, whereas the intracellular concentration of K^+ is 150 mmol/L, and typically

only 4–5 mmol/L in the extracellular fluids. This concentration differential, maintained by the (Na^+–K^+)-ATPase of the plasma membrane, ensures a number of major biological processes, such as cellular osmotic balance, signal transduction, and neurotransmission. (Na^+–K^+)-ATPase transports three Na^+ ions to the outside of the cell and two K^+ ions to the inside (Figs. 1.2 and 1.3), contributing to the action potential involved in transmission of nerve impulses along neuronal axons. Action potentials can be generated by presynaptic neurons at the rate of about 250 per second, accounting for between one-half and two-thirds of their total ATP consumption. The repetitive G-rich sequences found in the telomeres at the ends of eukaryotic chromosomes are stabilized by K^+ and Na^+ ions. The retention of Na^+ (hypernatremia) when Na^+ intake exceeds renal clearance is one of the most common electrolyte disorders in clinical medicine. Hyperkalemia has become more common in cardiovascular practice due to the growing population of patients with chronic kidney disease and the broad application of drugs that modulate renal elimination of potassium by reducing the production of angiotensin II.

The alkaline earth metal ions, Mg^{2+} and Ca^{2+}, have greater binding strengths to organic ligands than Na^+ and K^+, and therefore are less mobile. Both play important structural and catalytic roles, with 99% of the body's Ca^{2+} found in bone and teeth. Although Mg^{2+} is the least abundant of the "bulk elements," the intracellular concentration of free Mg^{2+} is around 0.5 mM, making it the most abundant cation, and less than 0.5% of total body Mg^{2+} is in the plasma. Half of cytosolic Mg^{2+} is bound to ATP and most of the rest, along with K^+, is bound to ribosomes. Unlike the other three bulk cations, Mg^{2+} has a much slower water exchange rate, allowing it to play a structural role, for example, participating in ATP binding in many enzymes involved in phosphoryl transfer reactions—6 of the 10 reactions of glycolysis are phosphoryl transfers.

Ca^{2+} serves as a messenger in virtually all of the important functions of cells. Why Ca^{2+} has ended up in this position is probably due to its unique coordination chemistry, which enables it to bind to sites of irregular geometry even in the presence of large excesses of other cations such as Mg^{2+} (Carafoli and Krebs, 2016). While the total Ca^{2+} concentration inside cells is micromolar, in the cytosol the concentration of free Ca^{2+} is about 10,000 times lower. This nanometer concentration is achieved by ligation of Ca^{2+} by two broad classes of specific proteins. (1) Those which buffer Ca^{2+} in the nanometer range, and in some cases, also process its information, by increasing, or less frequently decreasing, their biological activity upon Ca^{2+} binding by a change in conformation, illustrated for calmodulin in Fig. 1.4—"Ca^{2+} is not an active site metal, it is the allosteric metal par excellence" (Carafoli and Krebs, 2016). (2) Intrinsic membrane proteins which transport Ca^{2+} in or out of cells, or between the cytosol and the lumen of cellular organelles. Apoptosis (programmed cell death) plays a major role in the maintenance of tissue homeostasis. Ca^{2+}, in addition to its role in the regulation of cellular processes, may act as a proapoptotic agent, and both intracellular Ca^{2+} depletion or overload may trigger apoptosis (Brini et al., 2013). Hypercalcemia is a common metabolic perturbation and the increase in over-the-counter purchase of Ca^{2+} and vitamin D supplements, notably to combat osteoporosis in the aging population, is a contributory factor.

Of the six essential trace metal ions, Zn has ligand-binding constants intermediate between those of Mg^{2+} and Ca^{2+} and the other five. Manganese, iron, cobalt, copper, and molybdenum all have much stronger binding to organic ligands and are therefore only

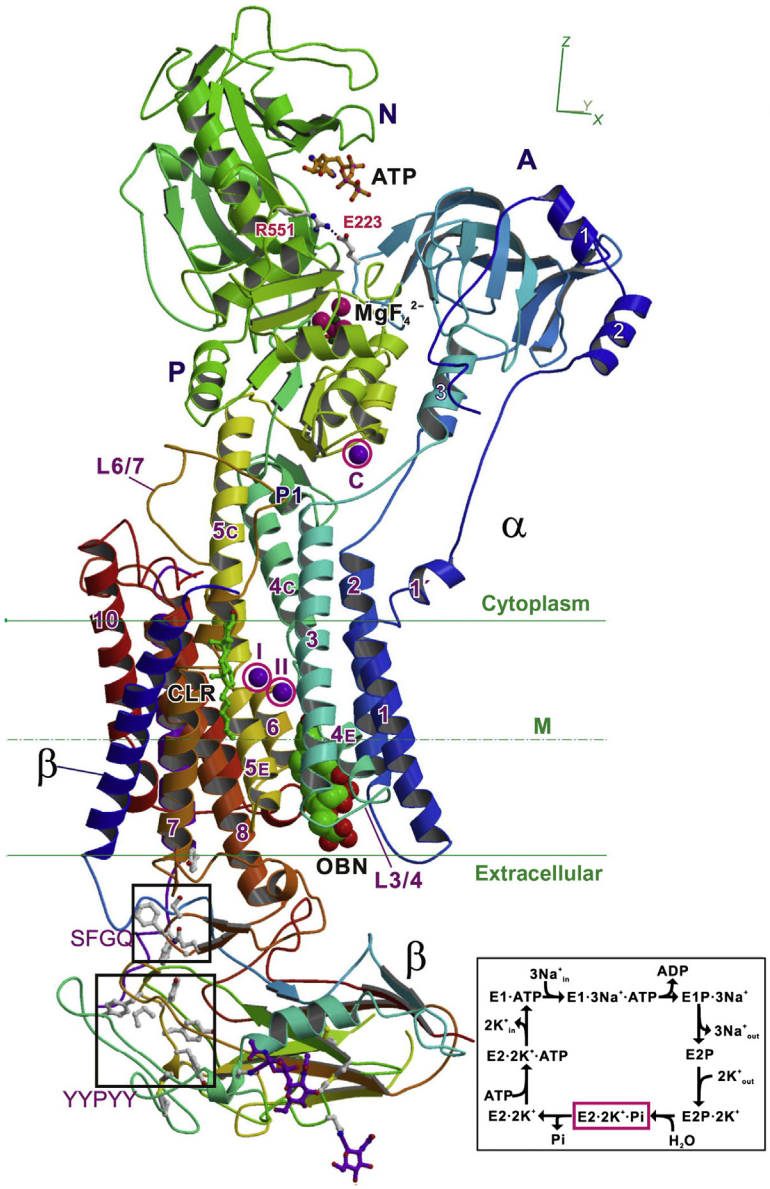

FIGURE 1.2 Architecture of Na^+,K^+-ATPase from shark rectal gland with bound MgF_4^{2-} and K^+, a stable analog of the $E2 \cdot P_i \cdot 2K^+$ state. A ribbon diagram of NKA with ouabain (shown in space fill) bound at low affinity (PDB ID: 3A3Y). Color changes gradually from the N-terminal (*blue*) to the C-terminal (*red*). ATP is taken from the $E2(TG) \cdot ATP$ crystal structure of Ca^{2+}-ATPase (SERCA1a) (PDB ID: 3AR4) and docked in the corresponding position. Bound K^+ ions are marked (I, II, and C) and circled. Inset shows a simplified diagram of the post-Albers scheme. *CLR*, cholesterol; *OBN*, ouabain. *Source: From Toyoshima et al. (2011). Copyright 2011. With permission from Elsevier.*

poorly mobile. In addition, they have access to at least two oxidation states, and therefore can participate in electron transfer and redox catalysis, whereas zinc has access only to the Zn^{2+} state.

Manganese can occur in biological systems in three oxidation states, Mn(II), Mn(III), and Mn(IV). In humans, manganese is essential for development, metabolism, and the antioxidant system through its involvement in a number of enzymes, including arginase,

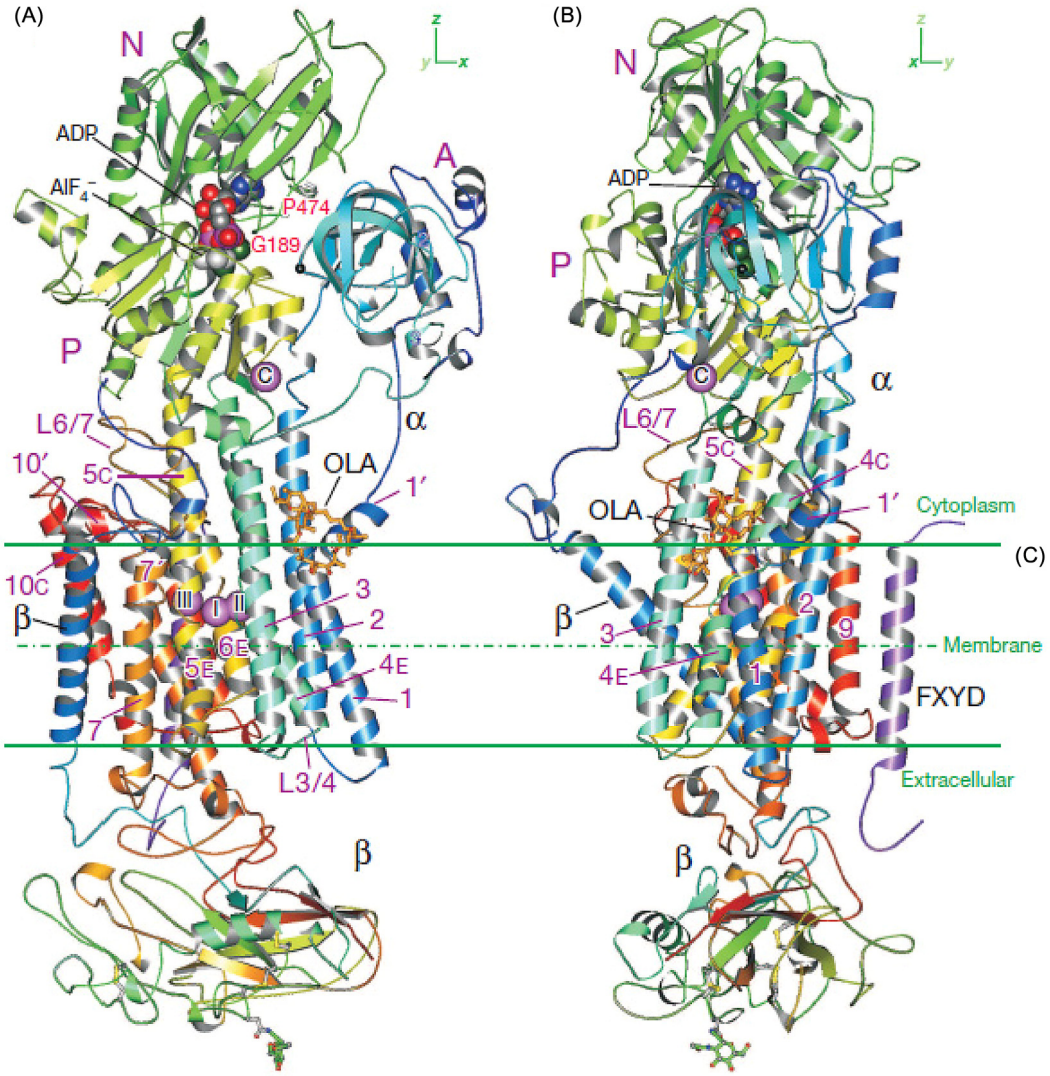

FIGURE 1.3 Crystal structure of Na^+, K^+-ATPase in the transition state analog $E1 \sim P \cdot ADP \cdot 3Na^+$. (A and B) Ribbon diagrams viewed in two orthogonal directions. Color changes gradually between the N terminus (*blue*) and C terminus (*red*) for the α- and β-subunits. *Purple* spheres show bound Na^+ ions [three (I–III) in the transmembrane region and one (C) in the cytoplasmic region]. Sugars attached to the β-subunit are shown as ball and stick. *OLA*, oligomycin A. *Source: From Kanai, R., Ogawa, H., Vilsen, B., Cornelius, F., Toyoshima, C., 2013. Crystal structure of a Na^+-bound Na^+, K^+-ATPase preceding the E1P state. Nature 502, 201–206. Copyright 2013. With permission from Elsevier.*

the enzyme responsible for urea production, mitochondrial superoxide dismutase, and glutamine synthetase, which plays an important role in the brain. Nevertheless, excessive exposure or intake may lead to a condition known as manganism, a neurodegenerative

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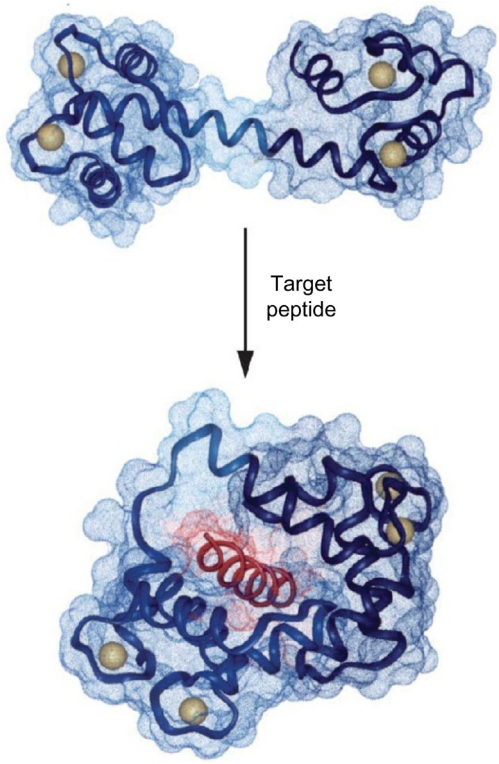

FIGURE 1.4 Ribbon representation showing how target binding induces changes in the quaternary structure of calmodulin. The conformation of the two domains of calmodulin is unaffected by target binding, but the orientation of the domains with respect to each other changes drastically, bringing the two previously independent domains into contact. Calcium-loaded calmodulin (PDB code 1CLL) is shown at the top and calcium-loaded calmodulin complexed with a peptide derived from smooth-muscle myosin light-chain kinase (PDB code 1CDL) is shown at the bottom. The N-terminal domain of calmodulin is *medium blue*, the C-terminal domain is *dark blue*, and the linker loop between the domains is *light blue*. The peptide is *red* and the calcium ions are represented as *yellow* balls. The tint indicates the Connolly surfaces of the molecules. *Source: From Johnson, C.N., Damo, S.M., Chazin, W.J., 2014. EF-hand calcium-binding proteins. In: Encyclopedia of Life Sciences. John Wiley & Sons Ltd., https://doi.org/10.1002/9780470015902.a0003056.pub3. Copyright 2014. With permission from John Wiley and Sons.*

disorder that causes dopaminergic neuronal death and parkinsonian-like symptoms (Avila et al., 2013). Clearly the most important role of manganese in biology is its involvement in the oxygen evolving complex of photosystem II in cyanobacteria, algae, and green plants, which oxidizes water into dioxygen, protons, and electrons (Eq. 1.1).

$$2\,H_2O \rightarrow 4H^+ + 4e^- + O_2 \tag{1.1}$$

The determination of the structure of the Mn_4CaO_5 cluster (Fig. 1.5) at the center of PSII (Suga et al., 2015) has provoked an intensive flurry of biomimetic chemistry, with the aim of generating "green energy" using our unlimited access to solar power (Najafpour et al., 2015).

Iron is the most abundant of the transition metal ions in humans, with the bulk present in the oxygen-binding heme proteins, hemoglobin and myoglobin. These both contain iron within the protoporphyrin IX nucleus, requiring a number of genes for biosynthesis of the porphyrin, insertion of iron, and subsequent heme transport (Crichton, 2016; Andreini et al., 2009). The remaining much smaller proportion of body iron is present in other iron-containing proteins (heme proteins, Fe–S proteins, and nonheme, non-Fe–S proteins) with a wide variety of functions, encoded by the human genome (Crichton, 2016). A recent bioinformatics approach indicates that about 2% of human genes encode an iron protein (48% heme-binding proteins, 17% Fe–S proteins, and 35% which bind individual iron ions).

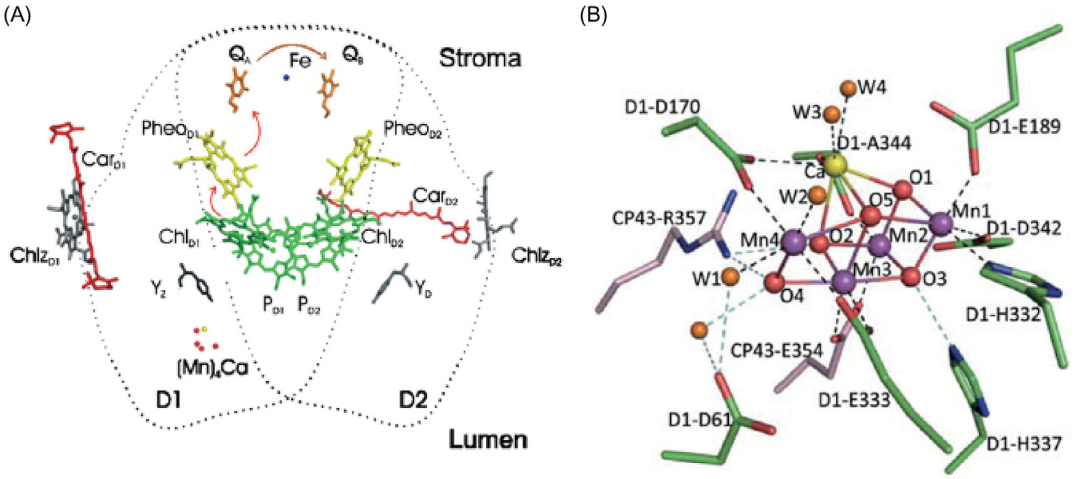

FIGURE 1.5 (A) Schematic representation of the cofactor arrangement in the core of the reaction center (the view is along the membrane plane). Organic cofactors (for the sake of simplicity, the heme group of cytochrome b_{559} is omitted) are colored *green* (Chl), *yellow* (Pheo), *magenta* (plastoquinones Q_A and Q_B), and *red* (carotenoids). Ca (*yellow*), Fe (*blue*), and Mn (*red*) are shown as spheres; the figure was generated using PyMOL (http://www.pymol.org). The coordinating protein subunits D1 and D2 are indicated by dotted lines. (B) Structural arrangement of the Mn_4CaO_x cluster and Mn−O, Ca−O, Mn−water, and Ca−water distances in the oxygen evolving complex (OEC) (in Å) Mn1, Mn2, Mn3, and Mn4 denote the different Mn ions of the OEC. *Source: (A) Reprinted with permission from Reger, G., 2012. Mechanism of light induced water splitting in photosystem II of oxygen evolving photosynthetic organisms. Biochim. Biophys. Acta 1817, 1164−1176. Copyright 2012 Elsevier. (B) Reprinted with permission from Suga, M., Akita, F., Hirata, K., Ueno, G., Murakami, H., et al., 2015. Native structure of photosystem II at 1.95 Å resolution viewed by femtosecond X-ray pulses. Nature 517, 99−103. Copyright 2015. Nature Publications.*

More than half of the human iron proteins have a catalytic function, and the authors estimate that 6.5% of all human enzymes are iron-dependent (Andreini et al., 2018).

Fe is a constituent of a large number of proteins involved in electron transfer chains in humans, notably the respiratory chain in the inner membrane of the mitochondria, involving cytochromes, Fe−S proteins, and quinines, channeling electrons to the terminal component, the Cu−Fe-dependent cytochrome *c* oxidase (COX) which mediates the reduction of O_2 (Eq. 1.2).

$$4H^+ + 4e^- + O_2 \rightarrow 2\,H_2O \tag{1.2}$$

Mammalian COX is composed of 13 subunits, three catalytic subunits I−III encoded by mitochondrial DNA, and 10 nuclear-coded subunits encoded by nuclear DNA (Fig. 1.6). Electrons from cytochrome *c* are transferred to the dimetallic Cu_A site, which rapidly reduces the heme *a*, some 19 Å away. Heme *a* then transfers electrons to the active site heme a_3 and Cu_B, where O_2 binds.

Copper is the third most abundant essential transition metal ion in the human body, involved, for example, in respiration, angiogenesis, and neuromodulation, yet Cu proteins represent less than 1% of the total proteome in both eukaryotes and prokaryotes

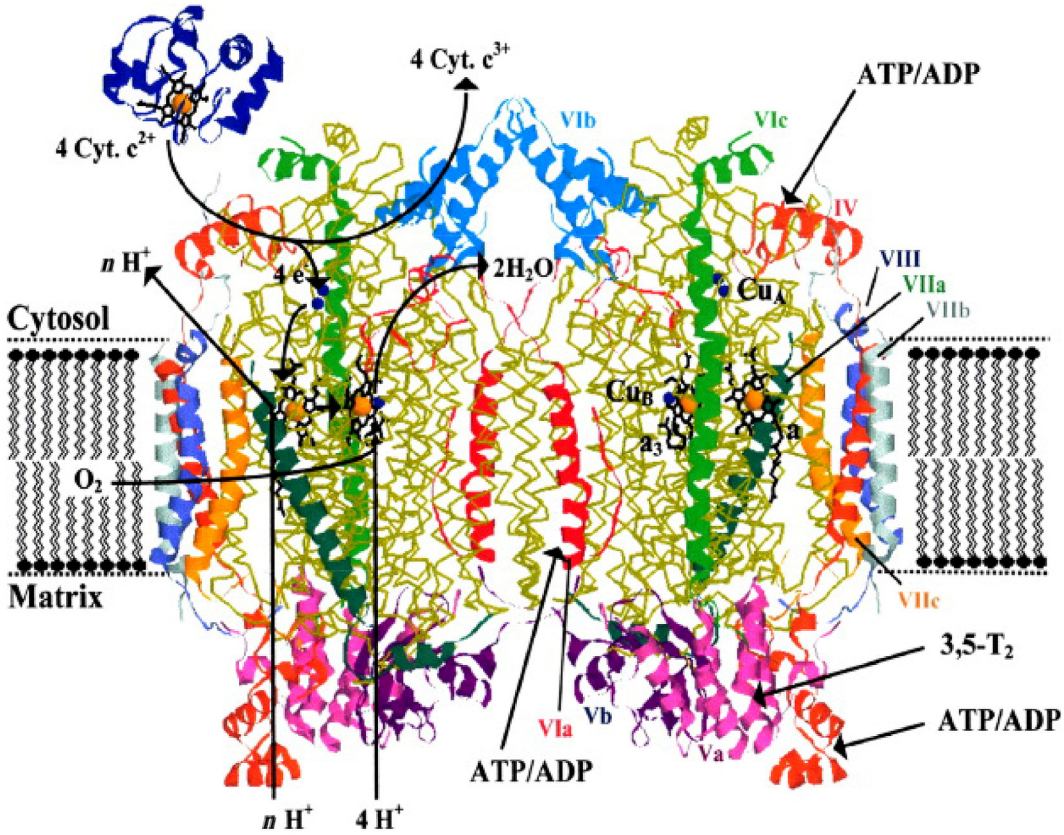

FIGURE 1.6 Crystal structure of dimeric cytochrome *c* oxidase from bovine heart (Tsukihara et al., 1996). The nuclear-coded subunits are in color, the mitochondrial-coded subunits I, II, and III are in *yellow*. Indicated schematically on the left monomer are the electron transport pathways from cytochrome *c* (Cyt. c) to oxygen accompanied by uptake of protons from the matrix for water formation and pumped protons (nH^+). On the right monomer binding sites for 3,5-diiodothyronine (T_2) and ATP or ADP are indicated. *Source: From Kadenbach, B., Hüttemann, M., 2015. The subunit composition and function of mammalian cytochrome* c *oxidase. Mitochondrion 24, 64–76. Copyright 2015. With permission from Elsevier.*

(Andreini et al., 2009). Copper sites in proteins can be classified as belonging to one of three classes. Type 1 (blue Cu proteins) function in single electron transfer, type II are catalytic sites which bind directly to substrates, while type III sites are dinuclear and are involved in the activation and transport of oxygen. The copper chaperones are a specific class of proteins which ensure the safe and specific delivery of potentially harmful copper ions to a variety of essential copper proteins (Palumaa, 2013). Cu is also involved as the catalytic component in detoxification (Cu/Zn superoxide dismutase).

Both iron and copper are characterized by genetic disorders associated with the accumulation of these metals in particular tissues, with toxic consequences. Wilson's disease is a chronic disease of the brain and liver due to a disturbance of copper metabolism,

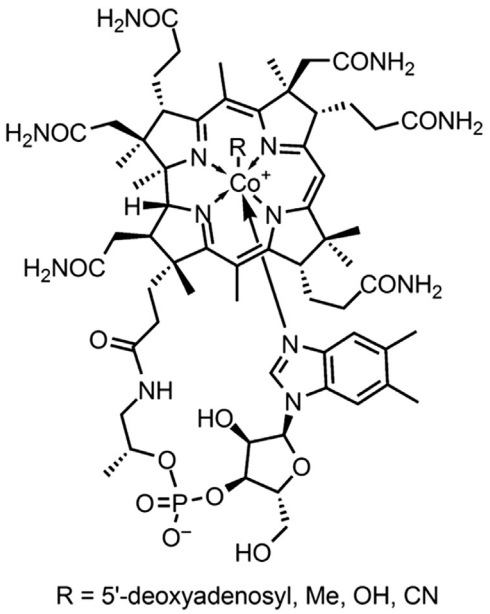

FIGURE 1.7 Structure of vitamin B_{12} shown as the Co^{3+} corrin complex, where R = 5′deoxyadenosyl, Me, OH^-, or CN^- (cyanocobalamin). *Source: With permission from Wikipedia (released into the public domain by its author Ymwang42 at the Wikipedia project).*

accompanied by progressive neurological dysfunction, with progressive accumulation of copper in the brain, liver, kidneys, and the cornea of the eye. Iron overload can result from genetic defects in iron absorption from the gastrointestinal tract (hereditary hemochromatosis), but can also result from genetic dysfunction of erythropoiesis, as in thalassemia, necessitating regular blood transfusions (secondary hemochromatosis).

Although only 1.6 mg is present in the human body, cobalt remains an essential trace element, and is required in the human diet in the form of cobalamin (vitamin B_{12}), a product of microbial biosynthesis, where the Co is tightly bound in a corrin ring (Fig. 1.7). Vitamin B_{12} uptake from the gut requires a specific protein, intrinsic factor, which is secreted by the gastric mucosa and is essential for efficient absorption of the vitamin. Lack of intrinsic factor causes pernicious anemia, and vitamin B_{12} was identified in 1925 as the antipernicious anemia factor. This is due to B_{12} being an essential cofactor for a number of B_{12}-dependent isomerases and methyltransferases (Banerjee et al., 2009) involved in DNA synthesis, amino acid and fatty acid metabolism, in the synthesis of myelin by oligodendrocytes wrapped around the axons of motor neurons, and in the maturation of developing red blood cells. Cobalt is acutely toxic in large doses and this was dramatically observed in the 1960s among heavy beer drinkers (15–30 pints/day), when Co^{2+} salts were added as foam stabilizers, resulting in severe and often lethal cardiomyopathy (Kesteloot et al., 1968).

Bioinformatics analysis of the human genome indicates that one protein in 10 (about 3000 in total) is a zinc metalloprotein (Andreini et al., 2006, 2009). Zn^{2+} is represented in all six classes of enzymes (as defined by the International Union of Biochemistry), where it can play both a structural as well as a catalytic role, often functioning like Mg^{2+} as a Lewis acid. It can also fulfill a very important regulatory function in the structural motifs

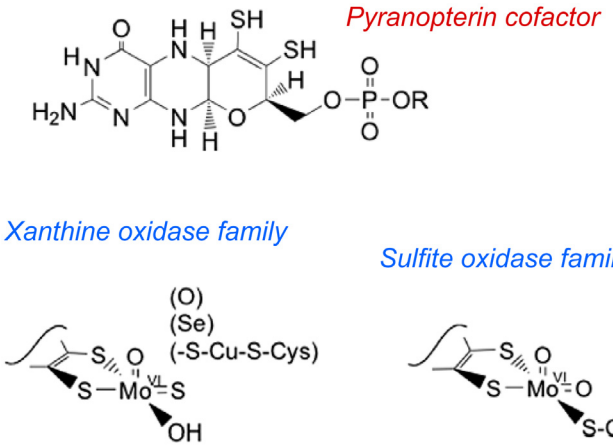

FIGURE 1.8 The structure of the pyranopterin cofactor common to all of these enzymes is given at the top. Active site structures for two families of mononuclear molybdenum enzymes (xanthine oxidase and sulfite oxidase). *Source: Reprinted with permission from Hille, R., Hall, J., Basu, P., 2014. The mononuclear molybdenum enzymes. Chem. Rev. 114, 3963–4038. Copyright 2014. American Chemical Society.*

known as "zinc fingers" involved in the regulation of transcription and translation by its binding to DNA and RNA. Zn^{2+} is the second most abundant of the trace metals (after iron), and is extensively involved in brain function, with mM concentrations in synaptic vesicles in which Zn is stored and from which it is released in a controlled manner (Bitanihirwe and Cunningham, 2009). In the course of meiotic maturation, oocytes take up over 2×10^9 zinc atoms, and when a sperm cell enters and fertilizes the oocyte, this triggers the coordinated release of zinc into the extracellular space in a prominent "zinc spark," detectable by fluorescence (Duncan et al., 2016). This loss of zinc is necessary to mediate the egg-to-embryo transition.

Although Mo is relatively rare in the Earth's crust, it is the most abundant transition metal in seawater, and since the oceans are as close as we get to the primordial soup in which life first evolved, it is no surprise that Mo has been widely used in biology. While Mo is well known as an important component of the FeMo cofactor in nitrogenase, the key enzyme of nitrogen-fixing organisms, there are a number of Mo-dependent enzymes in humans, which all contain Mo in the form of a molybdenum pyranopteridindithiolate cofactor (Fig. 1.8). These include xanthine oxidase, involved in the catabolism of purine bases, sulfite oxidase involved in sulfur metabolism, and aldehyde oxidase, involved in the metabolism of many drugs (Hille et al., 2014).

Ni, V, and Cr appear to be beneficial, and have been proposed to be essential for man. Although the human body contains around 8 mg of nickel, no Ni-dependent enzymes are known, however, it may be that Ni is essential for microorganisms that colonize the human gut (Zambelli et al., 2016).

Toxic metals

Essential metals can be toxic if excessive concentrations of the metal ions accumulate, often in specific tissues or organs—a number of examples of which are given above. However, as a consequence of environmental exposure, a number of nonessential metal

ions can accumulate within the body with toxic consequences. In what follows, we briefly describe some of the more common toxic metals.

While little credence is given today to the theory that Roman civilization collapsed as a result of chronic lead poisoning (saturnism), a recent study has shown that "tap water" from ancient Rome contained 100 times more Pb than local spring waters (Delile et al., 2014). We are now acutely aware that saturnism is a major environmental concern, and Pb exposure remains a widespread problem, particularly in the developing world. Pb toxicity affects several organ systems including the nervous, hematopoietic, renal, endocrine, and skeletal systems. It also causes behavioral and cognitive deficits during brain development in infants and young children. Pb appears to target proteins that naturally bind calcium and zinc, and examples include synaptotagmin, which acts as a calcium sensor in neurotransmission, and δ-aminolevulinate synthase (ALAD), the second enzyme in the heme biosynthetic pathway. Human ALAD is activated by Zn^{2+} with a K_m of 1.6 pM and inhibited by Pb^{2+} with a K_i of 0.07 pM. Pb^{2+} and Zn^{2+} appear to compete for a single metal-binding site (Simons, 1995).

The toxicity of cadmium manifested itself among the inhabitants of the Jinzu river basin in Japan in the 1950s due to environmental Cd pollution originating in effluent from a zinc mine located in the upper reaches of the river. In the Cd-polluted areas, 50%–70% of the Cd ingested orally was derived from rice. It remains the most severe example of chronic Cd poisoning caused by prolonged oral Cd ingestion. Cd^{2+} is a soft Lewis acid with a preference for easily oxidized soft ligands, particularly sulfur. It can displace Zn^{2+} from proteins where the Zn coordination environment is sulfur dominated, and given the similarity of its ionic radius with that of Ca^{2+} it can exchange with Ca^{2+} in calcium-binding proteins. Cadmium occurs in the environment naturally and as a pollutant emanating from industrial and agricultural sources. Exposure to cadmium in the nonsmoking population (there is a high concentration of Cd in cigarettes) occurs primarily through food, and chronic exposure results in respiratory disease, emphysema, renal failure, bone disorders, and immunosuppression.

The brutal reality of mercury toxicity was highlighted in 1956 by an environmental disaster which struck the population of Minamata, Japan, and its surroundings. Methylmercury was released in the industrial wastewater from a chemical factory and bioaccumulated in aquatic food chains, reaching its highest concentrations in shellfish and fish in Minamata Bay and the Shiranui Sea, which when eaten by the local population resulted in mercury poisoning. Of the 2265 victims officially recognized, 1784 died. The symptoms include ataxia, numbness in the hands and feet, general muscle weakness, narrowing of the field of vision, and damage to hearing and speech. The brain is the principal target tissue of MeHg and its major toxic effects are on the central nervous system, accumulating particularly in astrocytes. The biochemical target of Hg is the selenocysteine residues in selenoenzymes, as Hg has an affinity for Se ~1 million times greater than its affinity for sulfur (Ralston and Raymond, 2010, 2018). The selenoenzymes glutathione peroxidase, thioredoxin reductase, and thioredoxin glutathione reductase are required to prevent and reverse oxidative damage to the brain and neuroendocrine system, and they undergo irreversible inhibition by methylmercury (MeHg). Selenoenzyme inhibition appears likely to cause most if not all of the pathological effects of mercury toxicity, as outlined in Fig. 1.9.

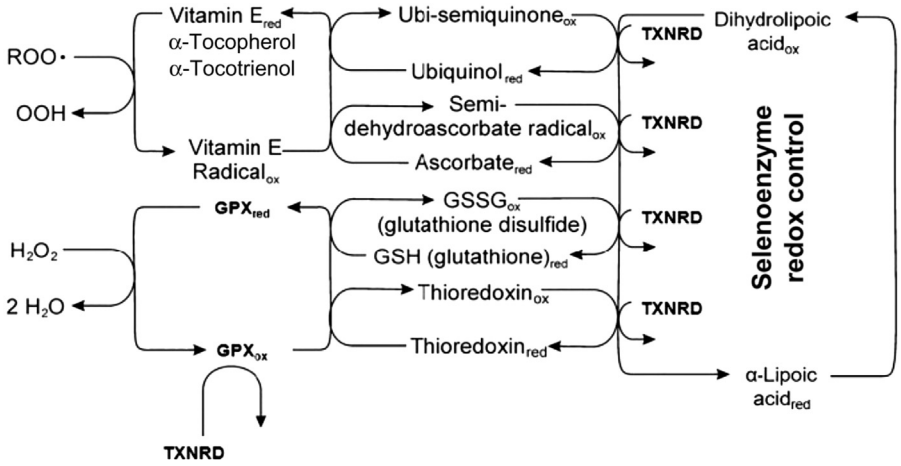

FIGURE 1.9 Se sequestration mechanism of Hg toxicity. A simplified portrayal of the normal cycle of selenoprotein synthesis is depicted on the left. Disruption of this cycle by exposure to toxic quantities of Hg (MeHg) is depicted on the right. Selenide freed during selenoprotein breakdown becomes bound to Hg, forming HgSe that accumulates in cellular lysosomes. If Hg is present in stoichiometric excess, formation of insoluble Hg selenides abolishes the bioavailability of Se for protein synthesis (indicated by gray text) and results in loss of normal physiological functions that require selenoenzyme activities. *Source: From Ralston, N.V., Raymond, L.J., 2018. Mercury's neurotoxicity is characterized by its disruption of selenium biochemistry. Biochim. Biophys. Acta Gen. Subj. 1862, 2405–2416.*

Despite comprising 8% of the Earth's crust, the most abundant metal and the third most abundant element after oxygen and silicon, aluminum is not used in biology; however, several factors have increased its access to the biosphere. First, an increase in anthropogenic acidification of soils, due to acid rain generated by emissions of sulfur dioxide and nitrogen oxides in the atmosphere, has resulted in elevated concentrations of Al^{3+} in ground waters. On account of its lightness and corrosion resistance, aluminum is widely used for industrial purposes, from the aerospace industry to construction, from food packaging to pharmaceuticals. Aluminum salts are extensively utilized as a flocculent in water treatment. This enhanced bioavailability has resulted in the accumulation of this metal in living organisms including humans, particularly in the skeletal system, the liver, and the brain. The toxicity of Al^{3+} is associated with anemia, osteomalacia, hepatic disorders, and certain neurological disorders. The molecular targets of Al toxicity involve disruption to the homeostasis of essential metal ions, notably Fe, Ca, and Mg. Al can replace Ca in bone and interfere with Ca-based signaling events, and can compete with Mg^{2+} binding to phosphate groups on cell membranes, ATP, and DNA. However, it is likely that the main targets of Al toxicity are Fe-dependent biological processes. Al^{3+} has coordination geometry similar to Fe^{3+}, which should enable Al^{3+} to subvert the plasma iron transport pathway. In the cytosol Al^{3+} is unlikely to be incorporated into ferritin, which requires redox cycling between Fe^{2+} and Fe^{3+}, and it seems likely that most aluminum accumulates in mitochondria, where it can interfere with Ca^{2+} homeostasis.

Metals in diagnosis and therapeutics

In addition to the essential metal ions, a large number of other metals, including some that are toxic, are routinely used in clinical medicine both as diagnostic and therapeutic agents, including gadolinium and technetium complexes used in their millions every year for diagnosis. The most widely used drugs for cancer chemotherapy are platinum complexes (Chellan and Sadler, 2015).

We begin by reviewing some of the growing number of metallo-organic complexes used for the noninvasive imaging techniques which have revolutionized modern medicine, allowing better diagnosis and greater patient comfort.

We begin with one of the oldest noninvasive diagnostic applications, the use of the relatively insoluble barium sulfate, $BaSO_4$, as a radiopaque contrast agent for X-ray imaging of the gastrointestinal tract.

In contrast, the metastable isotope of technetium, ^{99m}Tc, was first created in 1937 by cyclotron bombardment of molybdenum, It is a γ-emitter with a half-life of 6 hours, and is used in tens of millions of nuclear medicine imaging procedures every year. The 3D-scanning technique, single-photon emission computed tomography, uses a γ-camera which usually performs a full 360 degree rotation around the patient to obtain an optimal reconstruction. ^{99m}Tc is predominantly used for bone and brain scans. For the former, pertechnetate ions are used directly, as they are taken up by osteoblasts, while for brain scans ^{99m}Tc is chelated to hexamethylpropyleneamine oxime, which localizes in the brain according to regional blood flow. ^{99m}Tc scintigraphy can also be combined with computed tomography for more refined resolution.

Millions of doses of gadolinium are administered every year as MRI contrast agents. Gd (III) has high paramagnetism (seven unpaired electrons) and a favorable slow electronic relaxation time, which makes it effective in relaxing water protons which can generate contrast in MR images. Gd as the free ion is highly toxic even at low doses (10−20 μmol/kg), and for this reason it is necessary to use ligands that form stable complexes with the lanthanide ion. The high affinity of Gd toward polyaminocarboxylic acids has been exploited to form very stable complexes (up to $\log K_{ML} > 20$). The first contrast agent to be approved for clinical use was $[(Gd\text{-diethylene triamine penta-acetic acid (DTPA)})(H_2O)]^{2-}$ (Fig. 1.10) in 1988, which was administered to more than 20 million patients in the first 10 years of clinical experimentation.

Turning next to metals as drugs, pride of place must go to platinum. Currently around 50% of all cancer treatments involve Pt complexes, essentially the original drug cisplatin *cis*-$[PtCl_2(NH_3)_2]$, discovered in the 1960s and approved for clinical use in the late 1970s, and subsequently joined by its analogs carboplatin *cis*-[Pt(1,1-dicarboxycyclobutane)$(NH_3)_2$] and oxaliplatin [Pt(1*R*,2*R*-1,2-diaminocyclohexane)(oxalate)] (Fig. 1.11). Ruthenium complexes have also shown promise as anticancer drugs (Bergamo et al., 2012).

Lithium is the simplest therapeutic agent for the treatment of depression and has been used for more than 100 years. Lithium carbonate can reverse the symptoms of patients with bipolar disorder (manic-depression), a chronic disorder which affects between 1% and 2% of the population. This disease is characterized by episodic periods of elevated or depressed mood, severely reduces the patient's quality of life, and dramatically increases

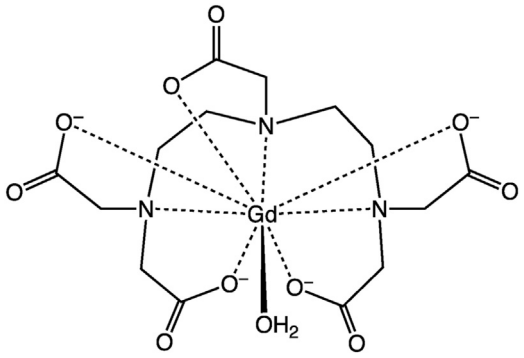

FIGURE 1.10 The structure of the MRI contrast agent Gd-DTPA (diethylene triamine penta-acetic acid). *Source: From Wikipedia www.LookForDiagnosis.*

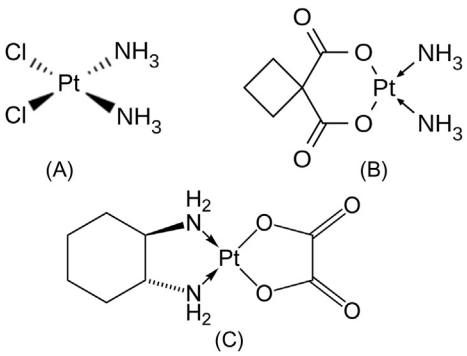

FIGURE 1.11 Platinum anticancer drugs approved for clinical use: (A) cisplatin; (B) carboplatin; and (C) oxaliplatin. *Source: From Wikipedia.*

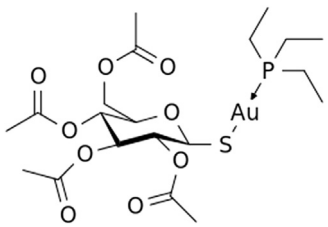

FIGURE 1.12 The orally active antirheumatoid arthritis drug Auranofin. *Source: From Wikipedia, by Ben Mills—own work, public domain, https://commons.wikimedia.org/w/index.php?curid = 5934319.*

their likelihood of committing suicide. Today, it is the standard treatment, often combined with other drugs, for bipolar disorder and is prescribed to over 50% of bipolar disorder patients. The molecular basis of mood disorder diseases and their relationship to the effects of lithium remain unknown.

Silver is well known for its potent antibacterial properties, and a combination of silver nitrate and a sulfonamide antibiotic as a topical antibacterial agent for burn management is still in use today, as are silver-containing wound dressings in lieu of antibiotics.

Gold has also been used as a drug since antiquity (Raubenheimer and Schmidbauer, 2014), with the Au(I) complex auranofin (Fig. 1.12) being developed for the treatment of rheumatoid arthritis as a substitute for the injectable gold compounds aurothiomalate and aurothioglucose. Despite efficacy in the treatment of both rheumatoid arthritis and

psoriasis, currently auranofin is seldom used as a treatment for patients with rheumatoid arthritis as more novel antirheumatic medications have become available. However, potential new applications of auranofin, notably for cancer therapy and treating infections including HIV, based on its dual inhibition of inflammatory pathways and thiol redox enzymes like mitochondrial thioredoxin reductase, have emerged (Madeira et al., 2012). Gold nanoparticles have great potential for controlled drug delivery, cancer treatment, biomedical imaging and diagnosis, and photothermal therapy (Elahi et al., 2018).

While there are many more examples of metals used as diagnostics or drugs, it seems appropriate to end this section by briefly mentioning the exciting development of theranostic agents (Terreno et al., 2012). These integrate diagnosis and therapy, allowing imaging-guided drug delivery, imaging of drug release, monitoring therapy by imaging, using theranostic agents for radiation-based therapies, and the use of imaging probes in imaging-guided surgery.

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public teaching of his word is associated with acts calculated to affect the mind with that solemnity which is the best preparation for hearing it to edification. It is thus that the ignorant and the vicious are collected together, and instructed and warned; the invitations of mercy are published to the guilty, and the sorrowful and afflicted are comforted. In these assemblies God, by his Holy Spirit, diffuses his vital and sanctifying influence, and takes the devout into a fellowship with himself, from which they derive strength to do and to suffer his will in the various scenes of life, while he there affords them a foretaste of the deep and hallowed pleasures which are reserved for them at his right hand for evermore. Prayers and intercessions are offered for national and public interests; and while the benefit of these exercises descends upon a country, all are kept sensible of the dependence of every public and personal interest upon God. Praise calls forth the grateful emotions, and gives cheerfulness to piety; and that instruction in righteousness which is so perpetually repeated, diffuses the principles of morality and religion throughout society; enlightens and gives activity to conscience; raises the standard of morals; attaches shame to vice, and praise to virtue; and thus exerts a powerfully purifying influence upon mankind. Laws thus receive a force, which, in other circumstances, they could not acquire, even were they enacted in as great perfection; and the administration of justice is aided by the strongest possible obligation and sanction being given to legal oaths. The domestic relations are rendered more strong and interesting by the very habit of the attendance of families upon the sacred services of the sanctuary of the Lord; and the rich and the poor meeting together, and standing on the same common ground as sinners before God, equally dependent upon him, and equally suing for his mercy, has a powerful, though often an insensible, influence in humbling the pride which is nourished by superior rank, and in raising the lower classes above abjectness of spirit, without injuring their humility. Piety, benevolence, and patriotism are equally dependent for their purity and vigour upon the regular and devout worship of God in the simplicity of the Christian dispensation.

The following is an abridgment of Dr. Neander's account of the mode of conducting public worship among the primitive Christians, which, though questionable on some points, is upon the whole just and interesting:--Since the religion of the New Testament did not admit of any peculiar outward priesthood, similar to that of the Old, the same outward kind of worship, dependent on certain places, times, and outward actions and demeanours, would also have no place in its composition. The kingdom of God, the temple of the Lord, were to be present, not in this or that place, but in every place where Christ himself is active in the Spirit, and where through him the worship of God in spirit and in truth is established. Every Christian in particular, and every church in general, were to represent a spiritual temple of the Lord; the true worship of God was to be only in the inward heart, and the whole life proceeding from such inward disposition, sanctified by faith, was to be a continued spiritual service; this is the great fundamental idea of the Gospel, which prevails throughout the New Testament, by which the whole outward appearance of religion was to assume a different form, and all that once was carnal was to be converted into spiritual, and ennobled. This notion came forward most strongly in the original inward life of the first Christians, particularly when contrasted with Judaism, and still more so when contrasted with Heathenism; a contrast which taught the Christians to avoid all pomp that caught the eye, and all multiplication of means of devotion addressed to the senses, while it made them hold fast the simple, spiritual character of the Christian worship of God. It was this which always struck the Heathen so much in the Christian worship; namely, that nothing was found among them of the outward pomp of all other religions; no temples, no altars, no images. This reproach was made to the Christians by Celsus, and answered thus by Origen: "In the highest sense the temple and image of God are in the human nature of Christ; and hence, also, in all the faithful, who are animated by the Spirit of Christ,--living images! with which no statue of Jove by Phidias is fit to be compared." Christianity impelled men frequently to seek for the stillness of the inward sanctuary, and here to pour forth their heart to God, who dwells in such temples; but then the flames

of love were also lighted in their hearts, which sought communion in order to strengthen each other mutually, and to unite themselves into one holy flame which pointed toward heaven. The communion of prayer and devotion was thought a source of sanctification, inasmuch as men knew that the Lord was present by his Spirit among those who were gathered together in his name; but then they were far from ascribing any peculiar sacredness and sanctity to the place of assembly. Such an idea would appear to partake of Heathenism; and men were at first in less danger of being seduced into such an idea, because the first general places of assembly of the Christians were only common rooms in private houses, just according as it happened that any member of the church had sufficient accommodation for the purpose. Thus Gaius of Corinth, Rom. xvi, is called the host of the church, because the church was in the habit of assembling in a room of his house. Origen says, "The place where believers come together to pray has something agreeable and useful about it;" but then he only says this in respect to that spiritual communion. Man, we must avow, is very easily led to fall away from the worship of God in spirit and in truth, and to connect the religion of the Spirit with outward and earthly things; as the Apostle says, "Having begun in the Spirit, to wish to end in the flesh." Watchfulness on this point was constantly needed, lest the Jewish or the Heathen notions should here intrude themselves on those of the Gospel, which was likely enough to happen as soon as the Old and the New Testament notions of the priesthood had been confused. Even in the time of Clemens of Alexandria he found himself obliged to combat the notion, which allowed the essentials of a Christian life to be of one kind in, and of another out of, the church. "The disciples of Christ," he says, "must form the whole course of their life and conduct on the model which they assume in the churches, for the sake of propriety; they must be such, and not merely seem so; as mild, as pious, and as charitable. But now, I know not how it is, they change their habits and their manners with the change of place, as the polypus, they say, changes its colour, and becomes like the rock on which it hangs. They lay aside the spiritual habit which they had assumed in the church, as soon as

they have left the church, and assimilate themselves to the multitude among whom they live. I should rather say, that they convict themselves of hypocrisy, and show what they really are in their inward nature, by laying aside the mask of piety which they had assumed; and while they honour the word of God, they leave it behind them in the place where they heard it."

The Christian places of assembly were, at first, in the rooms of private houses; it may perhaps be the case, that in large towns, where the number of Christians was soon considerable, and no member of the church had any room in his house sufficient to contain all his brethren, or in places where men did not fear any prejudicial consequences from large assemblies, the church divided itself into different sections, according to the habitations of its members, of which each section held its assemblies in one particular chamber of the house of some wealthy member of the church; or, perhaps, while it was usual to unite on Sundays in one general assembly, yet each individual part of the church met together daily in the rooms which lay the most convenient to it. Perhaps the passages in St. Paul's epistles, which speak of churches in the houses of particular persons, are thus to be understood. The answer of Justin Martyr to the question of the prefect, "Where do you assemble?" exactly corresponds to the genuine Christian spirit on this point. This answer was, "Where each one can and will. You believe, no doubt, that we all meet together in one place; but it is not so, for the God of the Christians is not shut up in a room, but, being invisible, he fills both heaven and earth, and is honoured every where by the faithful." Justin adds, that when he came to Rome, he was accustomed to dwell in one particular spot, and that those Christians who were instructed by him, and wished to hear his discourses, assembled at his house. He had not visited any other congregations of the church. The arrangements which the peculiarities of the Christian worship required, were gradually made in these places of assembly, such as an elevated seat for the purpose of reading the Scriptures and preaching, a table for the distribution of the sacrament, to which as early as the time of Tertullian the name of altar, *ara* or *altare*, was given, and perhaps

not without some mixture of the unevangelical Old Testament notion of a sacrifice; or at least this idea might easily attach itself to this name. When the churches increased, and their circumstances improved, there were, during the course of the third century, already separate church buildings for the Christians, as the name θρησκεύσιμοι τοπόι, [religious places,] of the Christians occurs in the edict of Gallienus. In the time of the external prosperity of the church, during the reign of Diocletian, many handsome churches arose in the great towns. The use of images was originally quite foreign to the Christian worship and churches, and it remained so during this whole period. The intermixture of art and religion, and the use of images for the latter, appeared to the first Christians a Heathenish practice. As in Heathenism the divine becomes desecrated and tarnished by intermixture with the natural; and as men have often paid homage to the beauties of nature, with injury to the cause of holiness, the first warmth of Christian zeal, which opposed the idolatry of nature, so common to Heathenism, and sought to maintain the divine in all its purity and elevation, was inclined rather to set holiness in the strongest contrast with what is beautiful by nature, than to endeavour to grace it by lending it a beautiful form. Men were more inclined in general to carry into extremes the idea of the appearance of the Divinity in the form of a servant, which suited the oppressed condition of the church in these centuries than to throw it into the back ground, and overwhelm it under the predominance of their æsthetic dispositions, and their love of art. This is peculiarly shown by the general belief of the early church, that Christ had clothed his inward divine glory in a mean outward form, which was in direct contradiction to it; a conclusion which was drawn from interpreting the prophecy of the Messiah in Isa. liii, 2, too literally. Thus, Clemens of Alexandria warns the Christians, from the example of Christ, not to attribute too much value to outward beauty: "The Lord himself was mean in outward form; and who is better than the Lord? But he revealed himself not in the beauty of the body, perceptible to our senses, but in the true beauty of the soul as well as of the body; the beauty of the soul consisting in benevolence, and that of the body in immortality!"

Fathers of entirely opposite habits of mind, the adherents of two different systems of conceiving divine things, were nevertheless united on this point by their common opposition to the mixture of the natural and the divine in Heathenism, and by the endeavour to maintain the devotion to God, in spirit and in truth, pure and undefiled. Clemens of Alexandria is as little favourable as Tertullian to the use of images. Heathens, who, like Alexander Severus, saw something divine in Christ's personal form, and sects which mixed Heathenism and Christianity together, were the first who made use of images of Christ; as, for instance, the Gnostic sect of the followers of Carpocratian, who put his image beside those of Plato and Aristotle. The use of religious images among the Christians did not proceed from their ecclesiastical but from their domestic life. In the intercourse of daily life, the Christians saw themselves every where surrounded by objects of Heathen mythology, or by such as shocked their moral and Christian feelings. Similar objects adorned the walls of chambers, the drinking vessels, and the signet rings, (on which the Heathen had constantly idolatrous images,) to which, whenever they pleased, they could address their devotions; and the Christians naturally felt themselves obliged to replace these objects, which wounded their moral and religious feelings, with others more suited to those feelings. Therefore, they gladly put the likeness of a shepherd carrying a lamb upon his shoulders, on their cups, as a symbol of the Redeemer, who saves the sinners that return to him, according to the parable in the Gospel. And Clemens of Alexandria says, in reference to the signet rings of the Christians, "Let our signet rings consist of a dove," the emblem of the Holy Ghost, "or a fish, or a ship sailing toward heaven," the emblem of the Christian church, or of individual Christian souls, "or a lyre," the emblem of Christian joy, "or an anchor," the emblem of Christian hope; "and he who is a fisherman, let him remember the Apostle, and the children who were dragged out from the water; for those men ought not to engrave idolatrous forms, to whom the use of them is forbidden; those can engrave no sword and no bow, who seek for peace; the friends of temperance cannot engrave drinking cups." And yet, perhaps, religious images made their way from domestic life into the

churches as early as the end of the third century, and the walls of the churches were painted in the same way. The council of Elvira set itself against this innovation as an abuse, for it made the following order: "Objects of reverence and worship shall not be painted on the walls." It is probable that the visible representation of the cross found its way very early into domestic and ecclesiastical life. This token was remarkably common among them; it was used to consecrate their rising and their going to bed, their going out and their coming in, and all the actions of daily life; it was the sign which Christians made involuntarily whenever any thing of a fearful nature surprised them. This was a mode of expressing, by means perceptible to the senses, the purely Christian idea, that all the actions of Christians, as well as the whole course of their life, must be sanctified by faith in the crucified Jesus, and by dependence upon him; and that this faith is the most powerful means of conquering all evil, and preserving oneself against it. But here also, again, men were too apt to confuse the idea and the token which represented it; and they attributed the effects of faith in the crucified Redeemer to the outward sign, to which they ascribed a supernatural, sanctifying, and preservative power; an error of which we find traces as early as the third century.

We now pass from the consideration of the places of public worship, to that of the seasons of worship, and the festivals of the early Christians. It is here shown again, that the Gospel, as it remodelled the former conceptions of the priesthood, of worship in general, and of holy places, also entirely changed the then views of sacred seasons. And here again, also, the character of the theocracy of the New Testament revealed itself, a theocracy spiritualized, ennobled, and freed from its outward garb of sense, and from the limits which bounded its generalization. The Jewish laws relating to their festivals were not merely abrogated by the Gospel, in such a manner as to transfer these festivals to different seasons; but they were entirely abolished, as far as fixing religious worship to particular times is concerned. St. Paul expressly declares all sanctifying of certain seasons, as far as men deduced this from the divine command, to be Jewish and unevangelical, and to be like

returning to the slavery of the law, and to captivity to outward precepts. Such was the opinion of the early church. At first the churches assembled every day; as, for instance, the first church of Jerusalem, which assembled daily for prayer in common, and for the public consideration of the divine word, for the common celebration of the Lord's Supper and the *agapæ*, as well as to maintain the connection between the common head of the spiritual body of the church and themselves, and between one another as members of this body. Traces of this are also found in later times in the daily assembling of the churches for the purpose of hearing the Scriptures read, and of celebrating the communion. Although, in order to meet the wants of human nature generally, consisting as it does of sense as well as soul, and those of a large body of Christians in particular, who were only in a state of education, and were to be brought up to the ripeness of Christian manhood, men soon selected definite times [beside the authorized Christian Sabbath, the first day of the week] for religious admonitions, and to consecrate them to a fuller occupation with religious things, as well as to public devotion, with the intention, that the influence of these definite times should animate and sanctify the rest of their lives, and that Christians who withdrew themselves from the distractions of business on these days, and collected their hearts before God in the stillness of solitude, as well as in public devotion, might make these seasons of service to the other parts of their life; yet this was in itself, and of itself, nothing unevangelical. It was only a dropping down from the purely spiritual point of view, on which even the Christian, as he still carries about two natures in himself, cannot always maintain himself, to the carnal; a dropping down which became constantly more necessary, the more the fire of the first animation and the warmth of the first love of the Christians died away. It was no more unevangelic than the gradual limitation of the exercise of many rights, belonging to the common priesthood of all Christians, to a certain class in the church, which circumstances rendered necessary. But just as the unevangelic made its appearance, men supposed certain days distinguished from others, and hallowed by divine right, when they introduced a distinction between holy and common days into the life

of the Christian, and in this distinction forgot his calling to sanctify all days alike. When the Montanists wished to introduce and make imperative new fasts, which were fixed to certain days, the Epistle to the Galatians was very properly brought to oppose them; but Tertullian, who stood on the boundary between the original pure evangelic times and those when the intermixture of Jewish and Christian notions first took place, confuses here the views of the two religions, because he makes the evangelical to consist, not in a wholly different method of considering festivals altogether, but in the celebration of different particular festivals; and he makes the Judaizing, which the Apostle condemns, to consist only in the observation of the Jewish instead of the peculiarly Christian festivals. The weekly and the yearly festivals originally arose from the self-same fundamental idea, which was the centre point of the whole Christian life; the idea of imitating Christ, the crucified and the risen; to follow him in his death, by appropriating to ourselves, in penitence and faith, the effects of his death, by dying to ourselves and to the world; to follow him in his resurrection, by rising again with him, by faith in him and by his power, to a new and holy life, devoted to God, which, beginning here below in the seed, is matured in heaven. Hence the festival of joy was the festival of the resurrection; and the preparation for it, the remembrance of the sufferings of Christ, with mortification and crucifixion of the flesh, was the day of fasting and penitence. Thus in the week the Sunday was the joyful festival; and the preparation for it was a day of penitence and prayer, consecrated to remembrance of the sufferings of Christ and the preparations for them, and this was celebrated on the Friday; and thus also the yearly festivals were to celebrate the resurrection of Christ, and the operations of the Redeemer after he had risen again; the preparation for this day was in commemoration of the sufferings and fastings of our Saviour. Allusion is made to Sunday under the character of a festival, as a symbol of a new life, consecrated to the Lord in opposition to the old Sabbath, in the epistle of Ignatius to the Magnesians: "If they who were brought up under the Old Testament have attained to a new hope, and no longer keep [Jewish] Sabbaths holy, but have consecrated their life

to the day of the Lord, on which also our life rose up in him, how shall we be able to live without him?" Sunday was distinguished as a day of joy by the circumstances, that men did not fast upon it, and that they prayed standing up and not kneeling, as Christ had raised up fallen man to heaven again through his resurrection. And farther: two other days in the week, Friday and Wednesday, particularly the former, were consecrated to the remembrance of the sufferings of Christ, and of the circumstances preparatory to them; congregations were held on them, and a fast till three o'clock in the afternoon, but nothing was positively appointed concerning them; in respect to joining in these solemnities every one consulted his own convenience or inclination. Such fasts, joined with prayer, were considered as the watches of the *milites Christi* [soldiers of Christ] on their post by the Christians, who compared their calling to a warfare, the *militia Christi*, and they were *stationes*, and the days on which they took place were called *dies stationum*, [day of their stations.] The churches, which were a graft of a Christian on a Jewish spirit, although they received the Sunday, retained also that of the Sabbath; and from them the custom spread abroad in the oriental church, of distinguishing this day, as well as the Sunday, by not fasting and by praying in an erect posture; in the western churches, particularly the Roman, where opposition to Judaism was the prevailing tendency, this very opposition produced the custom of celebrating the Saturday in particular as a fast day. This difference in customs would of course be striking, where members of the oriental church spent their Sabbath day in the western church. It was only too soon that men lost sight of the principle of the apostolic church, which retained the unity of faith and spirit in the bond of love, but allowed all kinds of difference in external things; and then they began to require uniformity in these things. The first yearly festivals of the Christians proceeded from similar views; and at first the contrast which had in early times the most powerful influence on the developement as well of the churchly life, as of the doctrines of Christianity, is peculiarly prominent; I mean the contrast between the Jewish churches and those of the Gentile converts. The former retained all the Jewish festivals as well as the whole ceremonial law;

although by degrees they introduced into them a Christian meaning which spontaneously offered itself. On the contrary, there was probably no yearly festival at all, from the beginning, among the Heathen converts; for no trace of any thing of the sort is found in the whole of the New Testament. The passover of the Old Testament was easily ennobled and converted to a passover which suited the New Testament, by merely substituting the idea of deliverance from spiritual bondage, that is, from the slavery of sin, for that of deliverance from earthly bondage. The paschal lamb was a type of Christ, by whom that deliverance was wrought. These representations went on the supposition, that Christ had partaken his last meal with his disciples, as a proper passover, at the very time that the Jews were celebrating theirs. This passover was, therefore, always celebrated on the night between the fourteenth and fifteenth of the Jewish month Nisan, as a remembrance at the same time of the last supper of Christ. This was the fundamental notion of the whole Jewish Christian passover, on which all the rest was built. The day following this passover was consecrated to the remembrance of the sufferings of Christ, and the third day from it to the remembrance of his resurrection. On the contrary, in the greater number of Heathen churches, as soon as men began to celebrate yearly festivals, (a time which cannot be determined very precisely,) they followed the method observed in the weekly festivals. They appointed one Sunday in the year for the festival of the resurrection, and one Friday as a day of penitence and fasting preparatory to this Sunday, in remembrance of the sufferings of Christ; and they gradually lengthened this time of penitence and fasting, as a preparation for that high and joyful festival. In these churches they were more inclined to take up a kind of antithetical turn against the Jewish festivals, than to graft Christian ones upon them. It was far from their notions to think of observing a yearly passover with the Jews. The following was the view which they took of the matter: "Every typical feast has lost its true meaning by the realization of that which is typified; in the sacrifice of Christ, the Lord's Supper, as the new covenant, has taken the place of that of the old covenant." This difference of outward customs between the Jewish Christian

churches and the churches allied to them on the one hand, and the Heathen Christian churches founded by St. Paul on the other, existed at first without its being supposed that external things of this nature were of importance enough to lead to a controversy. A fast formed the introduction to the passover; and this was the only fast formally established by the church. The necessity of this fast was deduced from Matthew ix, 15; but it was by a carnal interpretation of the passage, and an application of it quite contrary to its real sense. For it does not relate to the time of Christ's suffering, but to the time when he should be with his disciples no more. As long as they enjoyed his society they were to give themselves up to joy, and to be disturbed in it by no forced asceticism. But a time of sorrow was to follow this time of joy, although only for a season, after which a time of higher and imperishable joy, in invisible communion with him, was to follow, John xvi, 22. The duration of this fast, however, was not determined; the imitation of the temptation of our Lord for forty days introduced the custom of fasting forty hours in some places, which afterward was extended to forty days; and thus the fast of forty days, the quadrigesimal fast, arose. The festival of pentecost, Whitsuntide, was closely connected with that of the resurrection; and this was dedicated to commemorating the first visible effects of the operations of the glorified Christ upon human nature, now also ennobled by him, the lively proofs of his resurrection and reception into glory; and therefore Origen joins the festivals of the resurrection and of pentecost together as one whole. The means of transition from an Old Testament festival to one befitting the New Testament, were here near at hand. The first fruits of harvest in the kingdom of nature; the first fruits of harvest in the kingdom of grace; the law of the letter from Mount Sinai--the law of the Spirit from the heavenly Jerusalem. This festival originally embraced the whole season of fifty days from Easter, and was celebrated like a Sunday, that is to say, no fasts were kept during the whole of it, and men prayed standing, and not kneeling; and perhaps also in some places assemblies of the church were held, and the communion was celebrated every day. Afterward, two peculiar points of time, the ascension of Christ and the effusion of the Holy

Spirit, were selected from this whole interval. These were the only festivals generally celebrated at that time, as the passage cited from Origen proves. The fundamental notion of the whole Christian life, which referred every thing to the suffering, the resurrection, and the glorification of Christ, as well as the adherence, or, on the other hand, the opposition, to the Jewish celebration of festivals, were the cause that these were the only general festivals. The notion of a birth-day festival was far from the ideas of the Christians of this period in general; they looked upon the second birth as the true birth of men. The case must have been somewhat different with the birth of the Redeemer; human nature was to be sanctified by him from its first developement; but then this last notion could not at first come so prominently forward among the early Christians, because so many of them were first converted to Christianity when well advanced in years, after some decisive excitement of their life; but then it may have entered generally into domestic life, though at first gradually. Nevertheless, we find in this period apparently one trace of Christmas as a festival. Its history is intimately connected with the history of a kindred festival; the festival of the manifestation of Jesus in his character of Messiah, his consecration to the office of Messiah by the baptism of John, and the beginning of his public ministry as the Messiah, which was afterward called Epiphany, the ἑυρτη τῶν ἐπιφανίων, or τῆς ἐπιφανείας τοῦ Χριϛοῦ, [the festival of Epiphany, or of the appearance of Christ.] We find in later times that these festivals extended themselves in opposite directions, that of Christmas spreading from west to east, and the other from east to west. Clemens of Alexandria merely relates, that the Gnostic sect of the Basilidians celebrated the festival of the Epiphany at Alexandria in his time. We can hardly suppose that this sect invented the festival, although they may have had some dogmatical reason for celebrating it; for it is highly improbable that the catholic church should have afterward received a festival from the Gnostics; and these Gnostics most probably received it from the Jewish Christian churches in Palestine or Syria. For this time of our Saviour's life would appear the most important to the notions of the Jewish

Christians; and the Gnostics would afterward explain it according to their own ideas.

The character of a spiritual worship of God distinguished the Christian worship from that of other religions, which consisted in symbolical pageantry and lifeless ceremonies. As a general elevation of spirit and sanctification of heart was the object of every thing in this religion, instruction and edification, through a common study of the divine word, and through prayer in common, were the leading features in the Christian worship. And in this respect it might in its form adhere to the arrangements made about the congregations in the Jewish synagogues, in which also the element of a spiritual religious worship was the prevailing ingredient. As the reading of portions of the Old Testament had formed the ground work of religious instruction in the Jewish synagogues, this custom also passed into the Christian congregations. First the Old Testament, and especially the prophetic parts of it, were read as things that pointed to the Messiah; then followed the Gospels, and after that the epistles of the Apostles. The reading of the Scriptures was of still greater consequence then, because it was desirable that every Christian should be acquainted with them; and yet, by reason of the rarity and dearness of manuscripts, and the poverty of a great proportion of the Christians, or perhaps also because all were not able to read, the Bible itself could not be put into the hands of all. Frequent hearing was therefore with many to supply the place of their own reading. The Scriptures were therefore read in the language which all could understand, and that was, in most parts of the Roman empire, the Greek or the Latin. In very early times different translations of the Bible into Latin were in existence; as every one who knew a little of Greek, found it needful to have his own Bible in his own mother tongue. In places where the Greek or the Latin language was understood only by a part of the church, that is to say, by the educated classes, while the rest understood only their native language, as was the case in many Egyptian and Syrian towns, church interpreters were appointed, as in the Jewish synagogues, and they immediately translated what had been read into the language of the country, so that it might be intelligible to all.

After the reading of the Scripture there followed, as there had previously in the Jewish synagogues, short, and at first very simple, addresses in familiar language, the momentary effusions of the heart, which contained an explanation and application of what had just been read. Justin Martyr expresses himself thus on the subject: "After the reading of the Scriptures, the president instructs the people in a discourse, and incites them to the imitation of these good examples." Among the Greeks, where the taste was more rhetorical, the sermon from the very earliest times was of a more lengthened kind, and formed a very important part of the service. Singing also passed from the Jewish service into that of the Christian church. St. Paul exhorts the early churches to sing spiritual songs. What was used for this purpose were partly the Psalms of the Old Testament, and partly songs composed with this very object, especially songs of praise and thanks to God and Christ; and these, we know, Pliny found to be customary among the Christians. In the controversies with the Unitarians, about the end of the second century, and the beginning of the third, the hymns, in which from early times Christ had been honoured as a God, were appealed to. The power of church singing over the heart was soon recognized; and hence those who wished to propagate any peculiar opinions, like Bardasanes, or Paul of Samosata, endeavoured to spread them by means of hymns. In compliance with the infirmities of human nature, composed as it is of sense and spirit, the divine Founder of the church, beside his word, ordained two outward signs, as symbols of the invisible communion which existed between him, the Head of the spiritual body, and the faithful, its members; and also of the connection of these members, as with him, so also with one another. These were visible means to represent the invisible, heavenly benefits to be bestowed on the members of this body through him; and while man received in faith the sign presented to his senses, the enjoyment of that heavenly communion and those heavenly advantages was to gladden his inward heart. As nothing in all Christianity and in the whole Christian life stands isolated, but all forms one whole, proceeding from one centre, therefore, also, that which this outward sign represented must be something which

should continue through the whole of the inward Christian life, something which, spreading itself forth from this one moment over the whole Christian life, should be capable of being especially excited again and promoted in return, by the influence of isolated moments. Thus, baptism was to be the sign of a first entrance into communion with the Redeemer, and with the church, the first appropriation of those advantages which Christ has bestowed on man, namely, of the forgiveness of sins and the inward union of life, which proceeds from it, as well as of the participation in a sanctifying divine Spirit of life. And the Lord's Supper was to be the sign of a constant continuance in this communion, in the appropriation and enjoyment of these advantages; and thus were represented the essentials of the whole inward Christian life, in its earliest rise and its continued progress. The whole peculiar spirit of Christianity was particularly stamped in the mode in which these external things were administered; and the mode of their administration in return exerted a powerful influence on the whole nature of the Christian worship. The connection of the moments, represented by these signs, with the whole Christian life, the connection of inward and divine things with the outward act was present to the lively Christian feelings of the first Christians.

WRITING. In regard to alphabetic writing, all the ancient writers attribute the invention of it to some very early age, and some country of the east; but they do not pretend to designate precisely either the time or the place. They say, farther, that Cadmus introduced letters from Phenicia into Greece, if we may credit the Parisian Chronicle, B. C. 1519, that is, forty-five years after the death of Moses. Anticlides asserts, and attempts to prove, that letters were invented in Egypt fifteen years before Phoroneus, the most ancient king of Greece; that is, four hundred and nine years after the deluge, and in the one hundred and seventeenth year of Abraham. On this it may be remarked that they might have been introduced into Egypt at this time, but they had been previously invented by the Phenicians. Epigenes, who, in the estimation of Pliny, is weighty authority, informs us that observations, made upon the heavenly bodies for seven hundred and twenty years at Babylon, were written

down upon baked tiles; but Berosus and Critodemus, also referred to by Pliny, make the number of years four hundred and eighty. Pliny from these statements draws the conclusion that the use of letters, as he expresses it, must have been eternal, that is, beyond all records. Simplicius, who lived in the fifth century, states, on the authority of Porphyry, an acute historian, that Callisthenes, the companion of Alexander, found at Babylon a record of observations on the heavenly bodies for one thousand nine hundred and three years. Of course the record must have been begun B. C. 2234, that is, the eighty-ninth year of Abraham. This statement receives some confirmation from the fact that the month of March is called Adar in the Chaldaic dialect; and at the time mentioned, namely, the eighty-ninth year of Abraham, the sun, during the whole month of March, was in the sign of the zodiac called Aries, or the Ram. The word Adar means the same with Aries. But, as letters would be unquestionably first used for the purposes of general intercourse, they must have been known long before they were employed to transmit the motions of the stars. Of this we have an evidence in the bill of sale, which, as we have reason to suppose from the expressions used in Gen. xxiii, 20, was given to Abraham by the sons of Heth. Hence it is not at all wonderful that books and writings are spoken of in the time of Moses, as if well known, Exodus xvii, 14; xxiv, 4; xxviii, 9–11; xxxii, 32; xxxiv, 27, 28; Numbers xxxiii, 2; Deut. xxvii, 8. Nor is it a matter of surprise that long before his time there had been public scribes, who kept written genealogies: they were called by the Hebrews שוטרים, Exod. v, 14; Deut. xx, 5–9. Even in the time of Jacob, seals, upon which names are engraved in the east, were in use, Gen. xxxviii, 18; xii, 42; which is another probable testimony to the great antiquity of letters.

Letters, which had thus become known at the earliest period, were communicated by means of the Phenician merchants and colonies, and subsequently by Egyptian emigrants, through all the east and the west. A strong evidence of this is to be found in the different alphabets themselves, which betray by their resemblance a common origin. That the posterity of the Hebrew patriarchs preserved a knowledge of alphabetical writing during their abode in

Egypt, where essentially the same alphabet was in use, is evident from the fact, that the Hebrews while remaining there always had public genealogists. The law, also, was ordered to be inscribed on stones; a fact which implies a knowledge of alphabetical writing. The writing thus engraven upon stones is designated by its appropriate name, namely, חרות, Exodus xxxii, 16, 32. Not a few of the Hebrews might be unable to read and write, Judges viii, 14; but those who were capable of writing wrote for others, when necessary. Such persons were commonly priests, who, as they do to this day in the east, bear an inkhorn in their girdle, Ezek. x, 2, 3, 11. In the inkhorn were the materials for writing, and a knife for sharpening the pen, Jer. xxxvi, 23. The rich and noble had scribes of their own, and readers also; whence there is more frequent mention made of hearing than of reading, 1 Kings iv, 3; 2 Kings xii, 10; Isa. xxix, 18; Jer. xxxvi, 4; Rom. ii, 13; James v, 11; Rev. i, 3. The scribes took youth under their care, who learned from them the art of writing. Some of the scribes seem to have held public schools for instruction; some of which, under the care of Samuel and other prophets, became in time quite illustrious, and were called the schools of the prophets, 1 Sam. xix, 16, &c; 2 Kings ii, 3, 5; iv, 38; vi, 1. The disciples in these schools were not children or boys, but young men, who inhabited separate edifices, as is the case in the Persian academies. They were taught music and singing, and without doubt writing also, the Mosaic law and poetry. They were denominated, in reference to their instructers, the sons of the prophets; teachers and prophets being sometimes called fathers. After the captivity there were schools for instruction either near the synagogues or in them.

The materials and instruments of writing were, 1. The leaves of trees. 2. The bark of trees, from which, in the process of time, a sort of paper was manufactured. 3. A table of wood, πίναξ, לוח, Deut. ix, 9; Ezek. xxxvii, 5; Luke i, 63. In the east, these tables were not covered with wax as they were in the west; or at any rate very rarely so. 4. Linen was first used for the object in question at Rome. Linen books are mentioned by Livy. Cotton cloth also, which was used for the bandages of Egyptian mummies, and inscribed with hieroglyphics, was one of the materials for writing upon. 5. The

paper made from the reed papyrus, which, as Pliny has shown, was used before the Trojan war. 6. The skins of various animals; but they were poorly prepared for the purpose, until some improved methods of manufacture were invented at Pergamus, during the reign of Eumenes, about B. C. 300. Hence the skins of animals, prepared for writing, are called in Latin *pergamena*, in English parchment, to this day, from the city Pergamus. They are sometimes denominated in Greek, μεμβράνα, 2 Tim. iv, 13. 7. Tables of lead, עפרת, Job xix, 24. 8. Tables of brass, δέλτοι χαλκαὶ. Of all the materials, brass was considered among the most durable, and was employed for those inscriptions which were designed to last the longest, 1 Macc. viii, 22; xiv, 20–27. 9. Stones or rocks, upon which public laws, &c, were written. Sometimes the letters engraved were filled up with lime, Exod. xxiv, 12; xxxi, 18; xxxii, 19; xxxiv, 1; Deut. xxvii, 1–9; Joshua viii, 32; Job xix, 24. 10. Tiles. The inscriptions were made upon the tiles first, and afterward they were baked in the fire. They are yet to be found in the ruins of Babylon; others of later origin are to be found in many countries in the east. 11. The sand of the earth, in which the children in India to this day learn the art of writing, and in which Archimedes himself delineated his mathematical figures, John viii, 1–8. If in Ezekiel iii, 1, and in Revelation x, 9, we are informed that books were eaten, we must remember that the descriptions are figurative, and that they were eaten in vision; and consequently we are not at liberty to draw the conclusion from these passages, that any substance was used as materials for writing upon, which was at the same time used for food. The representations alluded to are symbolic, introduced to denote a communication or revelation from God.

As to the instruments used in writing, when it was necessary to write upon hard materials, as tables of stone and brass, the style was made of iron, and sometimes tipped with diamond, Jer. xvii. 1. The letters were formed upon tablets of wood, (when they were covered with wax,) with a style sharpened at one end, broad and smooth at the other; by means of which the letters, when badly written, might be rubbed out and the wax smoothed down. 2. Wax, however, was but rarely used for the purpose of covering writing

tables in warm regions. When this was not the case, the letters were painted on the wood with black tincture or ink. 3. On linen, cotton cloth, paper, skins, and parchment, the letters were painted with a very small brush, afterward with a reed, which was split. The orientals use this elegant instrument to the present day instead of a pen. *Ink*, called דיו, is spoken of in Num. v, 23, as well known and common, Jer. xxxvi, 18, and was prepared in various ways, which are related by Pliny. The most simple, and consequently the most ancient, method of preparation was a mixture of water with coals broken to pieces, or with soot, with an addition of gum. The ancients used other tinctures also; particularly, if we may credit Cicero and Persius, the ink extracted from the cuttle fish, although their assertion is in opposition to Pliny. The Hebrews went so far as to write their sacred books in gold, as we may learn from Josephus compared with Pliny.

Hieroglyphics, that is, sacred sculptures or engravings, received that appellation, because it was once, and indeed till very lately, thought, that they were used only to express, in a manner hidden from the vulgar, what was exclusively religious; and which it was thought proper to conceal from all but the learned. The fact, however, is, that the hieroglyphic was a kind of picture writing, which passed through various modifications, and was applied alike to sacred and to civil purposes; to the emblazonment of the attributes of idols, the exploits of warriors, and the events of illustrious history. Rudiments of the same art have been found among almost all savages. Among the semi-civilized Mexicans history was pictorial: and in Ceylon and Continental India the same vehicle of instruction is made use of on the walls of their temples, to convey moral lessons, or to indicate the character and exploits of their deities. In Egypt, however, the art was carried into a more perfect system, and was more ostensibly set before the public eye on the massive and almost eternal monuments which cover the country. There, too, it ascends to ages of the world with which the Scriptures have made us familiar, and stands associated with royal dynasties, and vicissitudes of conquest, more intimately blended with that stream of civil history, along the margin of which European education conducts

us. These mystic characters have acquired an adventitious interest also, from the circumstance that the key to them was for so many ages lost. This knowledge perished among that people themselves, the records of whose kings and conquests lay hid under the inexplicable symbol, or the fanciful representation of letters and sounds which were still familiar to the lips of those to whom the signs had become wholly unmeaning. Age after age they were gazed at by the curious; conjectures respecting their nature and use were offered by the learned, some absurd and some approaching the truth, but all failing to throw light upon a mystery, which at length was surrendered, by common consent, to the receptacle of lost and irrecoverable knowledge. Whether the hieroglyphics were symbols only, or words, or picturesque alphabetical characters, or expressed the popular tongue, or one known only to the priests, were questions answered at random by the prompt and dogmatic; and even the more modest and probable solutions of the cautious had so little collateral evidence to support them, that they led to no result. As to their intent, one thought that they involved the mysteries of magic; another, that they were a form of the Chinese language; a third, that they veiled the doctrines of the true patriarchal religion; a fourth, that they enveloped the dogmatic arcana of the Egyptian priesthood. The great point, however, to be determined was, whether the hieroglyphics were the signs of a language; that is, of the sounds of any language; and, if so, whether the language was now known, or knowable, from books still extant. Each of these points was of equal importance; for in vain would it have been ascertained that these signs represented the sounds of a tongue once spoken, if that tongue had perished from the earth. Clement of Alexandria, who lived about the end of the second century, asserted that the Egyptians had three modes of writing,--the epistolographic, or common characters; the hieratic, or sacerdotal, employed chiefly by the priesthood in writing books; and the hieroglyphic, used on public monuments. The symbolical he again distributes into imitative, which represent the plain figure of an object, as a circle to express the sun, and a half circle the moon; tropical,--which have recourse to analogy for the representation of the object; and

enigmatical,--as "a serpent, to signify the oblique course of the stars." This writer could not so accurately have expressed the truth of the case, unless he had known much more than he has written; and we may presume, that if he had been more liberal in his communications, the present age would not have had the honour of throwing open the gate to this branch of ancient learning. The notion which has generally prevailed, that by whatever rule the hieroglyphics were composed, they were invented by the Egyptian priests to conceal their wisdom from the vulgar, was combated by Bishop Warburton, with his usual acuteness. According to him, the first kind of hieroglyphics were mere pictures; because the most natural way of communicating our conceptions by marks or figures was, to trace out the images of things. But the hieroglyphics invented by the Egyptians were an improvement on this rude and inconvenient essay toward writing; for they contrived to make them both pictures and characters. He proceeds to other observations, which have lost their interest in consequence of the recent discoveries; but he argues conclusively, that hieroglyphics could not, in a vast number of cases, have been resorted to for purposes of secrecy, since they were employed to record openly and plainly their laws, history, and all kinds of civil matters. This, as a general view, has been proved to be correct; but still no key to the reading of these characters was found. The figures of deities might, in many instances, be deciphered by their attributes; other symbols were not difficult to explain, as they spoke a universal language. Thus two hands, one holding a bow, and another a shield, suggested a battle; an eye and a sceptre, a monarch of intelligence and vigilance; a ship and a pilot, the governor of a state if associated with a man, the ruler of the universe if associated with a deity. A lion was a natural emblem of strength and courage; a bullock, of agriculture; a horse, of liberty; a sphynx, of subtlety. But still those hieroglyphics were in the greatest number which appeared to represent letters; and many might prove, at the same time, both emblematic and alphabetical. Approaches to the truth of the case had been, indeed, made. Warburton, from an attentive perusal of what Clemens Alexandrinus had said on the subject, had, in fact, concluded, in a way highly

creditable to his acuteness, that hieroglyphics were a real written language, applicable to the purposes of history and common life, as well as to those of religion; and that, among the different sorts of hieroglyphics, the Egyptians possessed those which were used phonetically, or alphabetically, as letters; but, till recently, the means of following out this ingenious and correct conjecture were wanting to the learned. The first effectual step was taken by M. Quattermere, who proved, in his work *Sur la Langue et Littérature de l'Egypte*, [Concerning the Language and Literature of Egypt,] that the Coptic, a language of easy attainment, at least to a considerable extent, was the language of the ancient Egyptians. The second favouring circumstance of modern times was, the publication of the researches made as to the monuments of Egypt by the literary men and artists who accompanied the French expedition to that country. Previous to this, the specimens which had been brought to Europe were few, and the impressions and the fac similes of them incorrect. Some, too, were imitations, and others spurious. In the works published in France after this expedition, the representations of Egyptian monuments were numerous; and the inscriptions were given with perfect exactness and fidelity. Still, however, those would have remained as unintelligible as the originals but for the discovery of the Rosetta stone, now among the Egyptian antiquities in the gallery of the British museum. This stone was dug up by the French, near Rosetta, and contained an inscription in three sets of characters: one in hieroglyphics; a second in a sort of running hand, called enchorial, that is, in the common characters of the country; and a third in Greek. The latter appearing, from the disposition of the whole, to be a translation of the enchorial inscription, as that was of the hieroglyphic, the importance of this stone was at once seen by the French savans; but by the fortune of war, it was taken, with other valuables, by the British troops, and was sent to this country. The Antiquarian Society had it immediately engraved; and the fac similes, which were circulated through Europe attracted great attention. Dr. Young has, however, the honour of being the discoverer of the nature and use of the hieroglyphical inscription. M. de Sacy, and more especially Mr. Ackerblad, a Danish gentleman, made some

progress in identifying the sense of several parts of the second inscription, or that in demotic or enchorial characters, but made no progress in the hieroglyphics; and it was left for British industry to convert to permanent profit a monument which had been a useless, though a glorious, monument of British valour. The inscription upon this celebrated stone proved to be a decree of the Egyptian priests, solemnly assembled in the temple, to record upon a monument, as a public expression of their gratitude, all the events of the reign of Ptolemy Epiphanes; his liberality to the temples and to the gods; his success against his rebellious subjects; his clemency toward some of the traitors; his measures against the fatal consequences of excessive inundations of the Nile; and his munificence toward the college of the priests, by remitting the arrears of several years' payment of taxes. It was an important circumstance, that the whole concludes by ordering that this decree "shall be engraved on a hard stone in sacred characters, in common characters, and in Greek." By this it was ascertained that the second and third inscriptions were translations of the first; and that the second inscription was in the common character of the country. It was this that led Ackerblad to the investigation of the enchorial text, in order to discover its alphabet; in which he partially succeeded. His labours were, however, for some time unnoticed; but in 1814, Dr. Young published, in the Archæologia, an improvement on the alphabet of Ackerblad, and a translation of the Egyptian inscription. Difficulties of no ordinary kind, beside those arising from the mutilated state of the stone, presented themselves to all who had applied to make out even the second, or enchorial inscription.

"The method," says the Marquis Spineto, "pursued by our learned men in this Herculean task of deciphering the Rosetta stone, deserves to be noticed; it may serve to give you a proper idea of the infinite labour to which they have been obliged to submit; a labour which at first seemed calculated to deter the most indefatigable scholar. Figure to yourself, for a moment, the fashion introduced of writing the English language with the omission of most of its vowels, and then suppose our alphabet to be entirely lost or forgotten, a new mode of writing introduced, letters totally different from those

we use, and then conceive what our labour would be, if, after the lapse of fifteen hundred years, when the English language, by the operation of ages, and the intercourse with foreigners, was much altered from what it now is, we should be required, by the help of a Greek translation, to decipher a bill of parliament written in this old, forgotten, and persecuted alphabet, in every word of which we should find, and even this not always, the regular number of consonants, but most of the vowels left out. And yet this is precisely what our learned antiquarians have been obliged to do. The Egyptians, like most of the orientals, left out many of the vowels in writing. The enchorial, or demotic alphabet, which they used, has been laid aside since the second or third century of our era. From that time to this, that is, for nearly sixteen hundred years, the Coptic alphabet has been used; and yet in this Coptic language, and in these very enchorial or demotic characters, was engraved on the Rosetta stone the inscription which they have deciphered."

The steps of this interesting process are given by Dr. Young, in the Supplement to the Encyclopædia Britannica. The substance is as follows: "As the demotic characters showed something like the shape of letters, it was shrewdly suspected that they might have been used as an alphabet. By comparing, therefore, its different parts with each other, and with the Greek, it was observed that the two groups in the fourth and seventeenth lines of the Greek inscription, in which Alexander and Alexandria occur, corresponded with two other groups in the second and the tenth line of the demotic inscription. These two groups, therefore, were considered as representing these two names, and thus not less than seven characters, or letters, were ascertained. Again: it was observed that a small group of character occurs very often in almost every line. At first it was supposed that this group was either a termination, or some very common particle; and after some words had been identified, it was found to mean the conjunction *and*. It was then observed, that the next remarkable collection of characters was repeated twenty-nine or thirty times in the enchorial inscription; and nothing found to occur so often in the Greek, except the word king, which with its compounds, is repeated about thirty-seven times. A fourth assemblage of characters was

found fourteen times in the enchorial inscription, agreeing sufficiently well in frequency with the name of Ptolemy, which occurs eleven times in the Greek, and generally in passages corresponding to those of the enchorial text, in their relative situation; and, by a similar comparison, the name of Egypt was identified. Having thus obtained a sufficient number of common points of subdivision, the next step was to write the Greek text over the enchorial, in such a manner that the passages ascertained should coincide as nearly as possible; taking, however, a proper care to observe that the lines of the demotic or enchorial inscription are written from right to left, while those of the Greek run in a contrary direction from left to right. At first sight this difficulty seemed very great; but it was conquered by proper attention and practice; because, after some trouble, the division of the several words and phrases plainly indicated the direction in which they were to be read. Thus it was obvious that the intermediate parts of each inscription stood then very near to the corresponding passages of the other."

By means of the process above mentioned, Ackerblad, De Sacy, and Dr. Young, among whom a correspondence had been carried on, obtained a sort of alphabet from the enchorial characters, which might aid them in future researches. This result was published by Dr. Young in 1814. The examination of another stone at Menoup, containing an inscription in enchorial and in Greek characters, enabled Dr. Young to confirm the accuracy of former discoveries, and to add several new characters to the enchorial or demotic alphabet. Dr. Young next turned his attention to the hieroglyphics; and, though not with equal success, yet so as to demonstrate that they were phonetic or alphabetical, and to spell several proper names. The difficulty here, indeed, was how to begin; but his success opened a certain way to future progress; and it was upon Dr. Young's discovery that Champollion afterward engrafted his system, and was enabled to carry his researches into Egyptian antiquities and Egyptian hieroglyphics, to an extent which is now deeply engaging the attention of the literary world.

Two practical ends appear to have been answered already by the deciphering of the mystic monuments of Egypt. The first is, that the

inscriptions which have been read by Champollion, afford assistance in settling some questions of ancient chronology; the other is, that important collateral proof has been afforded of the historical accuracy of the Old Testament, and the antiquity of its books. It is presumptive in favour of the genuineness and antiquity of the writings of Moses, that such proper Egyptian names as are found in no other ancient writings beside his own, such as On, and Rameses, and Potipherah, and Asenath, should now be read in hieroglyphic characters on monuments still standing in the same country. But the confirmatory evidence goes still farther. In one inscription the names of two of the Pharaohs, Osorgon and Scheschonk, are exhibited. Of the characters which compose this legend some are phonetic, some figurative, and some symbolic. The whole reading in Coptic, is, "*Ouab an Amon-re soten annenoute Osorchon pri* (or *pre*) *ce* or *ci an ouab an Amon-re Souten Scheschonk-re Soten Nebto*, (*Amonmai Osorchon*,)" &c. The meaning of which is, "The pure by Amon-re, king of the gods, Osorchon deceased, son of the pure, by Amon-re, king of the gods, Scheschonk deceased, son of king of the world, (beloved by Amon-re, Osorchon,) imparting life, like the sun, for ever." This Osorchon seems to have been the Zarah, or Zarach, the king of Ethiopia, recorded in the Second Book of Chronicles, who, with a host of a thousand thousand and three hundred chariots, came to make war against Asa, the grandson of Jeroboam, and was defeated at Mareshah. Although the Greek historians have never mentioned either the name or exploits of Osorchon, this fact is attested by an hieroglyphical manuscript, published by Denon. It is a funeral legend, loaded with figures, on and round which there are several hieroglyphical inscriptions. With respect to the other Pharaoh, Champollion, speaking of the temple of Karnac, says, "In this marvellous place I saw the portraits of most of the ancient Pharaohs, known by their great actions. They are real portraits, represented a hundred times on the basso-relievos of the outer and inner walls. Each of them has his peculiar physiognomy, different from that of his predecessors and successors. Thus, in colossal representations, the sculpture of which is lively, grand, and heroic, more perfect than can be believed in Europe, we see the Pharaoh

Mandouei combating the nations hostile to Egypt, and returning triumphant to his country. Farther on, the campaigns of Rhamses Sesostris; elsewhere Sesonchis, or Shishak, dragging to the feet of the Theban Trinity, Ammon, Mouth, and Khous, the chiefs of thirty conquered nations, among which is found, written in letters at full length, the word *Joudahamalek*, that is, the kingdom of the Jews, or the kingdom of Judah. This is a commentary on the fourteenth chapter of the First Book of Kings, which relates the arrival of Shishak at Jerusalem, and his success there. Thus the identity between the Egyptian Sheschonk, the Sesonchis of Manetho, and the Sesac, or Schischak of the Bible, is confirmed in the most satisfactory manner."

YEAR. The Hebrews had always years, of twelve months each. But at the beginning, and in the time of Moses, these were solar years, of twelve months; each having thirty days, except the twelfth which had thirty-five. We see, by the reckoning that Moses gives us of the days of the deluge, Gen. vii, that the Hebrew year consisted of three hundred and sixty-five days. It is supposed that they had an intercalary month at the end of one hundred and twenty years; at which time the beginning of their year would be out of its place full thirty days. But it must be owned, that no mention is made in Scripture of the thirteenth month, or of any intercalation. It is not improbable that Moses retained the order of the Egyptian year, since he himself came out of Egypt, was born in that country, had been instructed and brought up there, and since the people of Israel, whose chief he was, had been for a long time accustomed to this kind of year. But the Egyptian year was solar, and consisted of twelve months of thirty days each, and that for a very long time before. After the time of Alexander the Great, and the reign of the Grecians in Asia, the Jews reckoned by lunar months, chiefly in what related to religion, and the order of the festivals. St. John, in his Revelation, xi, 2, 3; xii, 6, 14; xiii, 5, assigns but twelve hundred and sixty days to three years and a half, and consequently just thirty days to every month, and just three hundred and sixty days to every

year. Maimonides tells us, that the years of the Jews were solar, and their months lunar. Since the completing of the Talmud, they have made use of years that are purely lunar, having alternately a full month of thirty days, and then a defective month of twenty-nine days. And to accommodate this lunar year to the course of the sun, at the end of three years they intercalate a whole month after Adar; which intercalated month they call Ve-adar, or the second Adar.

The beginning of the year was various among different nations: the ancient Chaldeans, Babylonians, Medes, Persians, Armenians, and Syrians, began their year about the vernal equinox; and the Chinese in the east, and Latins and Romans in the west, originally followed the same usage. The Egyptians, and from them the Jews, began their civil year about the autumnal equinox. The Athenians and Greeks in general began theirs about the summer solstice; and the Chinese, and the Romans after Numa's correction, about the winter solstice. At which of these the primeval year, instituted at the creation, began, has been long contested among astronomers and chronologers. Philo, Eusebius, Cyril, Augustine, Abulfaragi, Kepler, Capellus, Simpson, Lange, and Jackson, contend for the vernal equinox; and Josephus, Scaliger, Petavius, Usher, Bedford, Kennedy, &c, for the autumnal. The weight of ancient authorities, and also of argument, seems to preponderate in favour of the former opinion. 1. All the ancient nations, except the Egyptians, began their civil year about the vernal equinox: but the deviation of the Egyptians from the general usage may easily be accounted for, from a local circumstance peculiar to their country; namely, that the annual inundation of the Nile rises to its greatest height at the autumnal equinox. 2. Josephus, the only ancient authority of any weight on the other side seems to be inconsistent with himself, in supposing that the deluge began in the second civil month, *Dius*, or *Marheshvan*, rather than in the second sacred month; because Moses, throughout the Pentateuch, uniformly adopts the sacred year; and fixes its first month by an indelible and unequivocal character, calling it *Abib*, as ushering in the season of green corn. And as Josephus calls the second month elsewhere *Artemisius*, or *Iar*, in conformity with Scripture, there is no reason why he should

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